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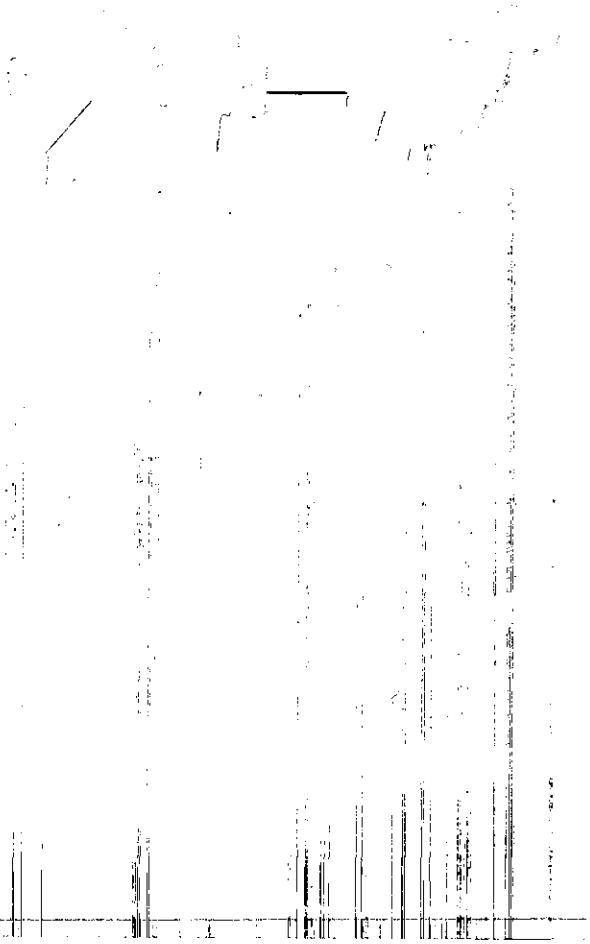

# ALKYLATION OF METAL ENOLATES OF UNSYMMETRICAL KETONES

A THESIS

Presented to

The Faculty of the Graduate Division

by

Byron Jerry Lee Huff

In Partial Fulfillment

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Doctor of Philosophy

in the School of Chemistry

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May, 1968

ALKYLATION OF METAL ENOLATES OF UNSYMMETRICAL KETONES

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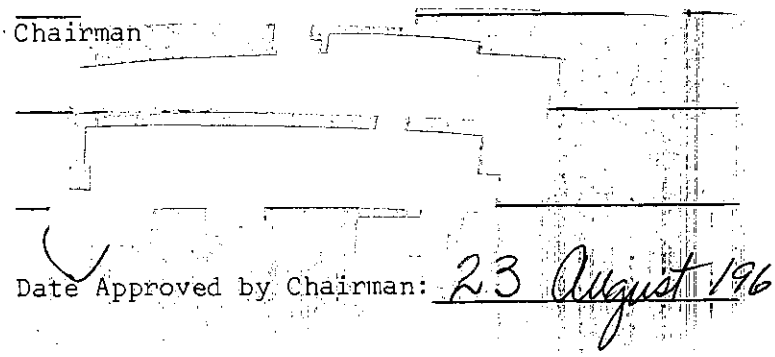

Chairman

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The author is indebted to his wife for her encouragement during the period of study.

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## GLOSSARY OF ABBREVIATIONS

| | |
|---|---|
| cps | cycles per second |
| DME | 1,2-dimethoxyethane |
| Dow-550 | Dowex 550 silicone (Dow Chemical) |
| ir | infrared |
| 4-MNP | 4-methyl-4-nitropimelonitrile |
| nmr | nuclear magnetic resonance |
| ppm | parts per million |
| SE-30 | silicone gum rubber (methyl) |
| SF-96 | silicone (General Electric) |
| THF | tetrahydrofuran |
| TMS | tetramethylsilane |
| VPC | vapor phase chromatography |
| XE-60 | silicone nitrile for VPC columns |

## SUMMARY

The primary aim of this research was to develop methods for alkylating an unsymmetrical ketone in a specific, predictable manner by investigating the properties of lithium enolates and their response to alkylation. The approach involved three avenues of investigation--the generation of specific metal enolates, the study of the kinetics of alkylation of suitable systems and the investigation of the stereochemistry of alkylation. Synthetic applications of lithium enolates have been developed and explored.

Because lithium enolates react with relatively reactive alkylating agents faster than they equilibrate by proton transfer reactions, reaction of unsymmetrical ketones with trityl lithium in DME offers a possible route to specific lithium enolates depending on the selectivity of proton removal. Indeed, trityl lithium exhibits significant selectivity in abstracting the proton from the less substituted position of unsymmetrical ketones, such as 2-methylcyclohexanone and cis-2-methyl-4-t-butylcyclohexanone in 1,2-dimethoxyethane. Trityl lithium, as well as trityl potassium, removes axial α-protons much faster than equatorial α-protons as shown by complete stereoselective formation of the less substituted enolate from trans-2-methyl-4-t-butylcyclohexanone in DME. Lithium enolates generated under kinetic conditions can be alkylated with many alkyl halides to give good yields of monoalkylated products in the same ratio in which the enolate anions are generated.

Reductive alkylation employing lithium in liquid ammonia provides a convenient means of synthesizing selectively alkylated cyclohexanone derivatives in cases where the necessary enones or α-haloketones are available. It provides distinct advantages over direct base-catalyzed alkylations of unsymmetrical ketones since such methods generally lead to mixtures of difficultly separable monoalkylation products as well as extensive di- and polyalkylation. This is the first example of an alkylation of the 3-alkylcyclohexanone system selectively *via* the $\Delta^{1(2)}$-enolate. The complete reduction of β-unsubstituted, α,β-unsaturated cyclohexanone derivatives requires one equivalent of an added proton donor, such as water or t-butyl alcohol.

Kinetics of ethylation of various cyclohexanones in DME indicates that ground state energy levels are a significant factor in determining alkylation rates in systems of comparable aggregation. The rates of ethylation of the lithium enolate of 2,2-dimethylcyclohexanone is faster than that of 2,6-dimethylcyclohexanone showing that steric interactions in the product are not controlling the energy of the transition state. The mechanism of alkylation consistent with all the observed kinetics is one involving reactive ion-pair species (one or more) in equilibrium with an unreactive aggregate. The free enolate anion is not a significant factor in the alkylation of lithium enolates of cyclohexanone derivatives with alkyl halides in DME.

Alkylation of 4-t-butylcyclohexanone and derivatives in DME demonstrates that chair and non-chair pathways for alkylation are both readily accessible. The transition state for alkylation resembles the

enolate anion and the interactions in the latter are more important than interactions in the product in controlling the rate and stereochemistry of alkylation.

# CHAPTER I

# INTRODUCTION

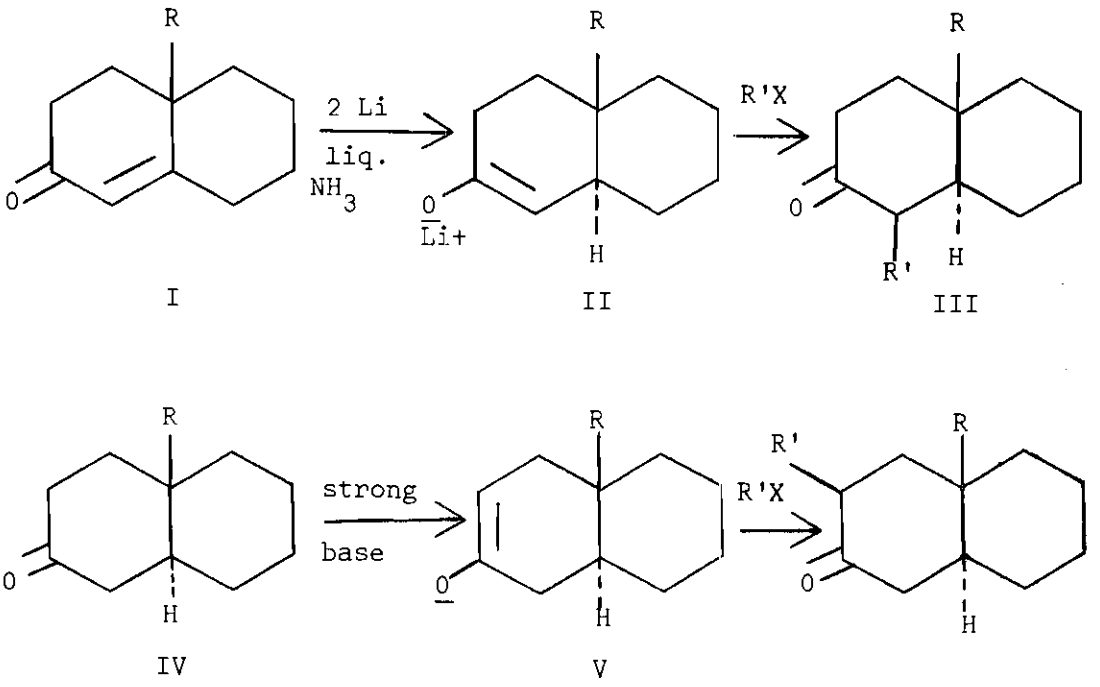
## Historical Background of Metal Enolate Alkylation

The desirability of alkylating a specific α-position in an unsymmetrical ketone in good yield has led to devising many ingenious schemes in order to accomplish a directed alkylation (1). The use of blocking groups, such as a benzylidene moiety (2) or a hydroxymethylene group substituted with N-methylaniline (3) or n-butyl mercaptan (4) has proven very successful in base-catalyzed alkylations to produce α,α-disubstituted derivatives. Hauser and co-workers (5) accomplished a specific alkylation by alkylating the dianion derived from an α-hydroxymethylene ketone. For example, all of the variations in the blocking group technique mentioned above have been employed to introduce an angular alkyl group in 1-decalone. In general, however, these techniques require multiple reaction sequences and often result in relatively low yields.

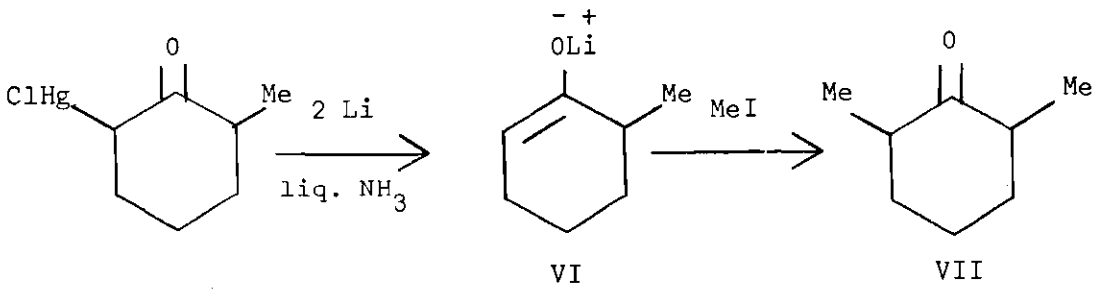
Formation of an α,α'-disubstituted ketone in base-catalyzed alkylation has been accomplished by employing an activating group, such as a carbethoxy or a formyl group. One of the most interesting methods for directing alkylation to the unsubstituted α-position in a 2-alkylcyclohexanone is alkylation of the halomagnesium salt of a cycloalkylimine of the ketone. For example, 2,6-dimethylcyclohexanone can be prepared in good yield from the bromomagnesium salt of the cyclohexyli-

mine of 2-methylcyclohexanone by reaction with methyl iodide (6). Enamines of unsymmetrical ketones have been used successfully to prepare α,α'-disubstituted ketones in a predictable manner (7).

Stork and co-workers (8) have shown that the lithium-ammonia reduction of α,β-unsaturated ketones of the type I leads to a specific lithium enolate II which can be alkylated in liquid ammonia to produce trans-1-alkyl-2-decalones. Significantly, the enolate II is the less stable one of the trans-2-decalone (IV) system (9), and direct alkylation of IV in the presence of a strong base yields a mixture consisting chiefly of 3-alkyl substituted products via the more stable enolate. Reductive alkylation has also been applied to steroid syntheses via α,β-unsaturated ketone functions (10,11). Weiss and co-workers (11) have applied reductive alkylation to α-bromo-,α-acetoxy- and α-hydroxy-steroidal ketones using sodium, calcium, and barium in addition to



lithium. Caine (12) generated a specific enolate VI by reducing 6-chloromercuri-2-methylcyclohexanone with lithium in liquid ammonia. After methylation 2,6-dimethylcyclohexanone was the only dimethyl product recovered. House and Trost (13) have also generated specific lithium enolates by reacting an enol acetate with two equivalents of methyl lithium; lithium t-butoxide is the by-product.

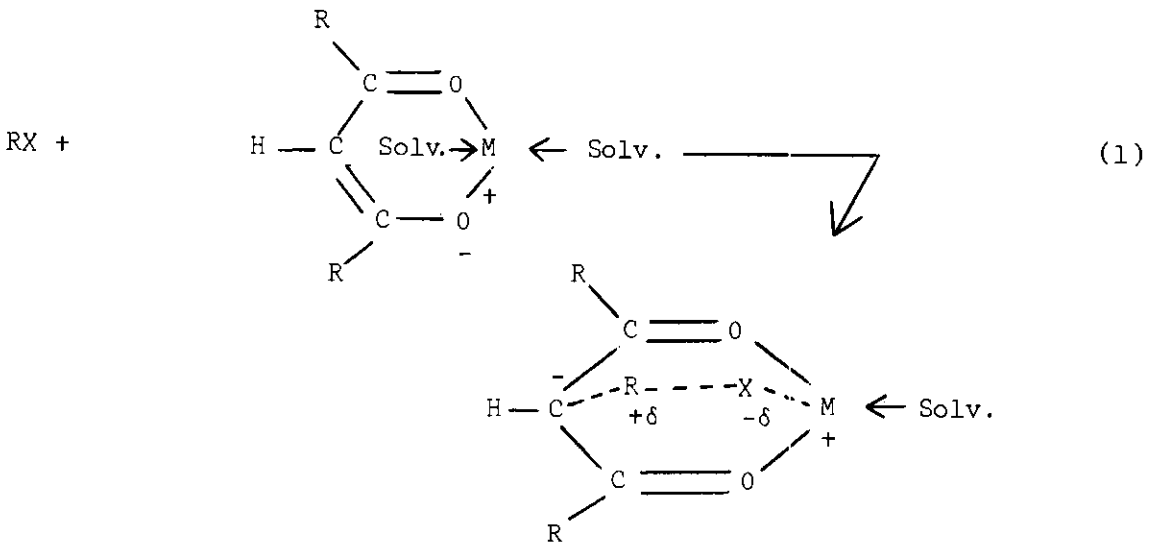



VI VII

Apparently, if a specific lithium enolate can be generated, it is possible to execute alkylations with reactive alkylating agents before the enolate anions equilibrate by proton exchange with initially alkylated neutral ketone. The slow equilibration rate of lithium enolates distinguishes them from other alkali metal enolates. It is well known (14) that, in the alkylation of unsymmetrical alicyclic ketones with alkyl halides in the presence of strong base, mixtures of products are obtained and that the monoalkylation product derived from reaction at the more highly substituted carbon atom predominates. For example, reaction of potassium enolates of 2-methylcyclohexanone with methyl iodide in 1,2-dimethoxyethane (12,15) yields a complicated mixture of products including VII, but 2,2-dimethylcyclohexanone is the major product and polyalkylation is significant. Many other examples

may be cited to show that sodium and potassium enolates of unsymmetrical ketones give complex mixtures derived from an equilibrium mixture of metal enolates (15,16). On the other hand, lithium enolates from unsymmetrical ketones generated under kinetic conditions with excess triphenylmethyl lithium in DME yield mixtures of alkylated products representing kinetic enolate compositions (12,17).

Regarding the essential nature of the alkylation reaction, much of the data and theory based on results from alkylation and acylation of β-diketo compounds has been summarized by Brandstrom (18). Apparently, the coordination of the halide to the metal ion is an essential step in the reaction as shown in Equation 1.




(1)

This may also account for the predominant C-alkylation in spite of the fact that the carbon atom bears a smaller fraction of the negative charge in the enolate anion and is more sterically hindered than the oxygen atom. The metal ion has a pronounced effect on the reaction particularly

with respect to rate. The potassium enolate of butyrophenone reacts with ethyl bromide in ether 6000-fold faster than the corresponding lithiobutyrophenone (19).

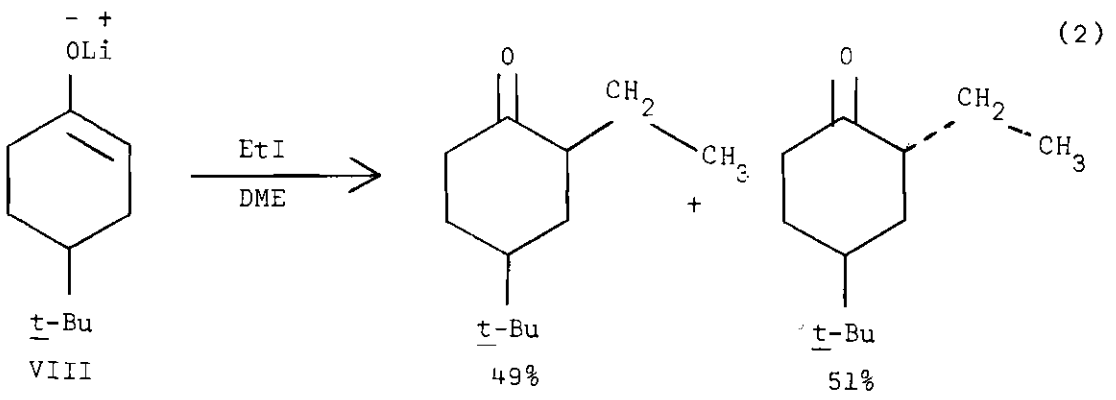
Another feature affecting profoundly the alkylation process is the solvent which determines the nature of the species undergoing alkylation in solution. The effect of solvent may be reflected in the rate of alkylation, the aggregation of metal enolates, and relative reactivities of both metal enolates and alkylating agents. The rate of butylation of the sodium derivative of diethyl n-butylmalonate with n-butyl bromide increases by an order of magnitude in going from benzene to tetrahydrofuran to DME to N,N-dimethylformamide or dimethyl sulfoxide. In fact, by adding small amounts of polar, aprotic solvents to the benzene both an increase in reaction rate and a kinetic dependence in additive with an order of between one and two have been observed (20). Because the sodio-n-butylmalonic ester exists in benzene as an ion-pair aggregate (association number > 40) (21), the polar additive enhances the reactivity by cleaving the aggregate into solvated ion-pair species in equilibrium with the original aggregate. No longer does the reaction depend solely on the particulate nature of an ion-pair aggregate. Zook and co-workers have shown that sodium enolates of butyrophenone in ether (19) and in DME (22) show an association number of 3 and 2.6, respectively.

Another important feature of the alkylation process is the nature of the alkylating agent and the changes in reactivity with changes in alkyl group and leaving group. Zook and Rellahan (23) have observed in

the alkylation of sodium enolates of butyrophenone in ether that the order of reactivity of alkyl bromides with α-branching is in the order methyl > ethyl >> isopropyl < t-butyl and with β-branching ethyl > propyl > isobutyl >> neopentyl. Conia (24) has observed that the reactivity toward alkylating agents of the sodium enolate of 2-methylcyclohexanone in benzene or toluene with respect to various leaving groups is as follows: alkylsulfate ≈ tosylate > iodide > bromide > chloride. Thus, the facts support a postulated bimolecular nucleophilic substitution mechanism; although the rates of alkylation with tertiary or benzyl halides indicate that there is a significant $S_N1$ contribution to the transition state for alkylation in these cases. In addition, the free enolate anion is not involved significantly in most ether and hydrocarbon solvents (19) and even in some dipolar, aprotic solvents (25).

The stereochemistry of alkylation is the other salient feature of the alkylation reaction that is very important in synthetic applications and in explaining the principal characteristics of the transition state. If, as is postulated (26), alkylation of a metal enolate obeys the principle of maximum overlap of reacting orbitals (27), then the alkylating agent is constrained to attack the metal enolate in the direction perpendicular to the plane which contains the α-carbon being alkylated and the carbon and oxygen of the original carbonyl group. For a cyclohexanone system attack on the enolate from one direction gives a product initially in the chair conformation with the new group axial. Attack from the opposite direction results in a product in a twist conformation which can interconvert to produce a chair with the new group

equatorial. Although it is generally assumed that chair-axial attack is favored for simple cyclohexanones based on interactions in the product, experimental evidence indicates that the alternate path is competitive (28) and in some cases favored (29). From the results of ethylation of 4-t-butylcyclohexanone lithium enolate in DME, House and co-workers (30) have concluded that each path is energetically favorable and that the transition state for alkylation resembles the enolate anion.* Equation 2 indicates that virtually equal amounts of cis- and trans-2-ethyl-4-t-butylcyclohexanone were obtained on ethylating VIII.




(2)

*This conclusion regarding the nature of the transition state based on the results of kinetic and stereochemical studies performed in this research had been reported on two occasions prior to the publication of Reference 30. See Reference 31 b,d.

## Outline and Purpose of the Research

The aim of the present research was to develop methods for alkylating an unsymmetrical ketone in a specific, predictable manner by investigating the properties of lithium enolates and further elucidating the nature of the alkylation process. A direct base-catalyzed alkylation scheme for a specific position in an unsymmetrical ketone would be a valuable contribution to synthetic organic chemistry. The approach involved three avenues of investigation--the generation of specific metal enolates, the study of the kinetics of alkylation of suitable systems and the investigation of the stereochemistry of alkylation. Synthetic applications of lithium enolates have been developed and explored. Portions of this research have been published or formally presented (31).

# CHAPTER II

## INSTRUMENTATION AND EQUIPMENT

Melting points were determined on a Fisher-Johns hot stage melting point apparatus and are uncorrected. Carbon and hydrogen microanalyses were performed by Galbraith Laboratories, Knoxville, Tennessee. Deuterium microanalyses were obtained by Dr. J. Nemeth (Urbana, Illinois) using a falling-drop method. Mass spectral data were obtained using a Varian M-66 mass spectrometer. A Perkin-Elmer, Model 137, recording spectrophotometer was employed to acquire the bulk of the infrared spectra using 0.2 mm sodium chloride solvent cells or sodium chloride plates. A Perkin-Elmer, Model 457, recording spectrophotometer was used to obtain a few infrared spectra. Generally, only absorptions characteristic of the functional groups present were listed. All proton magnetic resonance spectra were obtained from a Varian, Model A-60, high resolution spectrometer. Carbon tetrachloride (unless otherwise noted) containing tetramethylsilane (TMS) as an internal standard was used as the solvent. Chemical shifts are presented in ppm (unless otherwise noted) down-field from the standard. The abbreviations s, d, t, q, and m refer to singlet, doublet, triplet, quartet, and multiplet, respectively; coupling constants (J) are given in Hz.

Evaporations of solvents were carried out under reduced pressure using a rotating evaporator. Vapor phase chromatography was performed

using an Aerograph Manual Temperature Programmer Gas Chromatograph, Model A-90-P. In a few instances an F & M Dual Column Gas Chromatograph, Model 700, was used. Anhydrous sodium sulfate or anhydrous magnesium sulfate was employed as the drying agent in working up reactions. Reagent grade inorganic chemicals were used in this research except in certain specified cases. A Hanovia 450-watt immersion light source in a quartz water jacket was used for the photochemical experiments. Finally all temperatures refer to the Centigrade scale.

# CHAPTER III

# EXPERIMENTAL

## Generation of Specific Metal Enolates

### Preparation of Starting Materials

Solvents, Alkylating Agents, and Acylating Agents. The preparation of both 1,2-dimethoxyethane and tetrahydrofuran involved fractionation through a six-foot column packed with glass helices, storage in a dark bottle, drying at reflux over lithium aluminum hydride and distillation prior to use. Diethyl ether, the commercial anhydrous product, was dried by reflux over $LiAlH_4$ and distilled prior to use. Methyl iodide was dried over calcium chloride and distilled into a receiver protected from light. Acetic anhydride was freshly distilled immediately prior to use.

Phenyl Lithium. Phenyl lithium was prepared by the method of Gilman and Morton (32) or purchased from Alfa Inorganics, Inc., as a 2 M solution in 70:30 benzene:ether. Solutions of phenyl lithium were stored in a refrigerator (about 10°).

2-Methylcyclohexanone (IX). Compound IX was purchased from Aldrich Chemical Co., or prepared by the procedure of Johnson and coworkers (33).

2,2-Dimethylcyclohexanone (X). Under a positive nitrogen pressure 500 ml of liquid ammonia was distilled from sodium and condensed with a Dry Ice and acetone condenser. Next, 3.18 g (0.455 mol) of

lithium wire was introduced and allowed to dissolve by stirring the mixture for 15 min. A solution containing 20.0 g (0.182 mol) of 2-methyl-2-cyclohexen-1-one, 3.28 g (0.182 mol) of water, and 100 ml of anhydrous DME was added to the lithium-ammonia solution over a period of 90 min. The deep blue color persisted after the addition, and the mixture was stirred for one hour. At this time 250 ml of dry ether was introduced as rapidly as condensation of ammonia would allow to serve as a co-solvent for alkylation. A solution of 102 g (0.73 mol) of methyl iodide in 100 ml of dry ether was added dropwise over a period of one hour, and the ammonia was allowed to evaporate overnight. The slurry that remained was combined with 100 ml of ether and 200 ml of brine. After separating the phases the aqueous fraction was extracted with four 75-ml portions of ether. The combined ethereal solutions were washed with 100 ml of three per cent hydrochloric acid solution, 100 ml of saturated aqueous sodium bicarbonate solution, and 75 ml of water. The ethereal extract was dried ($MgSO_4$); the material was distilled to yield 10.0 g (43.7%) X: bp 78-81° (30 mm) (lit. (34a) 169-170° (768 mm)); ir (film) 1705 (C=O) and 1378, 1360 $cm^{-1}$ ($C(CH_3)_2$); nmr ($CCl_4$) $\delta$ 2.5-2.1 (broad absorption, 2, $CH_2CO$), 2.0-1.5 (broad absorption, 6), and 1.05 ppm (s,6,$C(CH_3)_2$) (12). VPC analysis (10-ft x 0.25-in column, 20% SE-30 on 60/80 firebrick, 120°, 60 ml/min) indicated > 95% purity with traces of IX and 2,2,6-trimethylcyclohexanone.

2,6-Dimethylcyclohexanone (VII). Compound VII was prepared according to the general procedure of Johnson and co-workers (33). A solution containing 60 ml of water, 13.56 g (0.046 mol) of technical

sodium dichromate dihydrate, 8.5 ml of conc. sulfuric acid and 5.7 ml of glacial acetic acid was added dropwise with stirring over a 2.5-hr period to a solution of 14.02 g (0.111 mol) of 2,6-dimethylcyclohexanol in 60 ml of distilled stock benzene. The temperature of the mixture was maintained at 7-10° by intermittent use of an ice bath. After the addition of the oxidant, stirring was continued for three hours followed by addition of the mixture to 100 ml of benzene and 100 ml of water. The resulting emulsion was subjected to vacuum filtration with the recovery of a small amount of amorphous solid. The phases were then separated, and the aqueous layer was extracted with three 75-ml portions of benzene. The combined benzene solutions were washed with 100 ml of water, 100 ml of saturated aqueous sodium bicarbonate solution and 75 ml of brine, respectively. The benzene extracts were dried; the material was distilled to yield 10.8 g (77%) of VII: bp 168-170° (760 mm) (lit. (34b) 170-172° (760 mm)); ir (film) 1700 $cm^{-1}$ (C=O); nmr ($CCl_4$) identical with that reported previously (12). VPC analysis (10-ft x 0.25-in column, 20% SE-30 on 60/80 firebrick, 120°, 60 ml/min) indicated only one product with equal retention time to that of authentic VII.

2-Methyl-4-t-butylcyclohexanone (93% cis) (XI). Compound XI was prepared by the method of Conia and Briet (35) in 23% yield. VPC analysis (10-ft x 0.25--in column, 15% 4-methyl-4-nitropimelonitrile (4-MNP) on acid washed firebrick, 60 ml/min, 170°) indicated 93% cis-XI and 7% trans-XI with no other products. All spectral data were identical to those reported by Conia and Briet (35).

2-Methyl-4-t-butylcyclohexanone (75% trans) (XI). Malhotra and Johnson (36) reported that essentially all trans-XI could be prepared by kinetic hydrolysis of the pyrrolidine enamine of XI. The enamine (37) was prepared under nitrogen by refluxing a solution of 12.0 g (0.071 mol) of XI and 12 ml of pyrrolidine (shaken with KOH and freshly distilled) in 60 ml of benzene for 48 hrs using a Dean-Stark apparatus to provide constant water separation. After removal of the solvent *in vacuo*, the material was distilled yielding 4 g of XI and 10.5 g (67%) of material, bp 79-85°(0.1 mm). Although the compound was not characterized completely, the nmr spectrum was consistent with the structure of N-(trans-2-methyl-4-t-butylcyclohex-6-enyl)-pyrrolidine. The nmr spectrum was recorded as follows: ($C_6H_6$, solvent and refrerence) -186 (m, 1, NC=C$\underline{H}$), -258 (m, 4, $C\underline{H}_2NC\underline{H}_2$), -269 to -341 (broad absorption, 10), -364 (d, 3, J=7 Hz, $CHC\underline{H}_3$), and -379 cps (s, 9, $C(C\underline{H}_3)_3$). The freshly distilled enamine (10.5 g, 0.047 mol) was transferred in total to 250 ml of diglyme (refluxed over calcium hydride and freshly distilled) under nitrogen and 10.0 g (0.083 mol HOAc) of 50% acetic acid was dripped into the solution over a period of three minutes with stirring.* After ten additional minutes the entire solution was added to 250 ml of water and 250 ml of ether. The ethereal solution was removed; the aqueous phase was extracted with four 125-ml portions of ether. The combined ethereal solutions were washed with 125 ml of water, 125 ml of saturated aqueous sodium bicarbonate, and 100 ml of

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*Dr. S. K. Malhotra kindly furnished the experimental details for the enamine hydrolysis.

brine, consecutively. The ethereal solution was dried ($MgSO_4$); distillation yielded 5.6 g (71%) of XI, bp 60-65° (0.5 mm); nmr ($CCl_4$) $\delta$ 2.7-1.2 (broad absorption, 7), 1.10 (d, 2.3, J=7 Hz, axial $CHC\underline{H}_3$), 0.93 (d, 0.7, J=6 Hz, equatorial $CHC\underline{H}_3$), 0.92 ppm (s, 9, $C(C\underline{H}_3)_3$); nmr ($C_6H_6$) $\delta$ 0.80 (s, $C(C\underline{H}_3)_3$) and 1.00 ppm (d, J=7 Hz, $CHC\underline{H}_3$). VPC analysis (10-ft x 0.25-in column, 15% 4-MNP on firebrick, 170°, 60 ml/min) showed 75% trans-XI and 25% cis-XI.

2-Methyl-2-Cyclohexen-1-one (XII). 2-Methyl-2-cyclohexen-1-one, bp 85-87° (35 mm) (lit. (33) bp 83-85.5° (35 mm)), was prepared in 41% yield by the procedure of Warnhoff, Martin, and Johnson (33). The infrared (38) and nmr (39) spectra agreed with those previously reported.

6-Methyl-2-cyclohexen-1-one (XIII). 6-Methyl-2-cyclohexen-1-one, bp 70-72° (25 mm)(lit. (40) 74-75° (24 mm)), was prepared in 29% yield by the procedure of Stork and White (40). The infrared spectrum was identical with that previously reported (41). The nmr spectrum was as follows: nmr (neat, external TMS) $\delta$ 6.63 (12 lines d, t, d, 1, $J_{AB}$=10 Hz (42), J'=4 Hz, J"=1 Hz, COCH=C$\underline{H}$), 5.57 (6 lines, d, d, d, 1, $J_{AB}$=10 Hz, J'=J"=2 Hz, COC$\underline{H}$=CH), 2.33-1.17 (broad absorption, 5) and 0.77 ppm (d, 3, J=7 Hz, $CHC\underline{H}_3$).

3-Methyl-2-cyclohexen-1-one (XIV). 3-Methyl-2-cyclohexen-1-one was purchased from Aldrich Chemical Co. The infrared (38) and nmr (43) spectra were identical to those previously reported.

7β-Isopropyl-10α-methyl-$\Delta^{1(9)}$-octalone-2 (XV). Compound XV was prepared by the procedure of Stork, Djerassi, *et al.*, (44) in 64% yield based on unrecovered D-(+)-carvomenthone (45). The infrared (44) spectrum agreed with that published previously.

4,4,6-Trimethyl-2-cyclohexen-1-one (XVI). Alkylation of the 6-hydroxymethylene derivative of 4,4-dimethyl-2-cyclohexen-1-one* was employed for the synthesis of XVI using the general procedure of Mariella (46). To a stirred mixture of 12.3 g (0.23 mol) of sodium methoxide and 400 ml of anhydrous ether in a 1-l three-necked flask purged with nitrogen and cooled in an ice bath, a solution of 18.3 g (0.25 mol) of ethyl formate (refluxed for one hour over phosphorus pentoxide and freshly distilled) and 28.1 g (0.23 mol) of 4,4-dimethyl-2-cyclohexen-1-one was added dropwise with stirring over one hour. The ice bath was removed and the reaction mixture was stirred overnight at the ambient temperature. After the addition of 200 ml of anhydrous ether, the slurry was filtered using a Buechner funnel, and the filter cake was washed with several portions of dry ether. The solid sodioformyl ketone was dissolved in 500 ml of water, and the ethereal filtrate was extracted with three 150-ml portions of 3% aqueous sodium hydroxide. The caustic extracts and the aqueous solution were then combined, washed with two 100-ml portions of ether and acidified with 15% hydrochloric acid solution. Crude 6-hydroxymethylene-4,4-dimethyl-2-cyclohexen-1-one was obtained after extraction of the acidic mixture with three 250-ml portions of ether, drying of the ether solution over anhydrous magnesium sulfate, and removal of the solvent under reduced pressure. The crude product, 19.0 g, was then added to a mixture of 500 ml of anhydrous

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*Dr. H. A. Smith prepared 4,4-dimethyl-2-cyclohexen-1-one by the procedure of Stork and co-workers (7) and kindly supplied it.

acetone (47), 17.3 g (0.13 mol) of potassium carbonate, and 42.6 g (0.30 mol) of methyl iodide, and the reaction mixture was refluxed for 24 hrs (an additional 20-ml portion of methyl iodide was added to the reaction mixture at 2-, 6-, and 19-hr intervals). The reaction mixture was then cooled to room temperature and anhydrous ether was added until no precipitation occurred on further addition. The solid was removed by filtration and the volume of the filtrate reduced to about 100 ml under reduced pressure. After the addition of 600 ml of ether, the solution was extracted with two 150-ml portions of ice-cold 10% sodium hydroxide and washed with 2% hydrochloric acid, aqueous sodium bicarbonate, and aqueous sodium chloride. The ethereal extract was dried, concentrated, and distilled giving 5.8 g of XVI*: bp 55-57° (2.0 mm); ir ($CCl_4$) 1675 (C=O) and 1610 $cm^{-1}$ (C=C); nmr ($CCl_4$) $\delta$ 6.55 (42) (4 lines, d, d, 1, $J_{AB}$=10 Hz, J'=1 Hz, COCH=C$\underline{H}$), 5.59 (d, 1, $J_{AB}$=10 Hz, COC$\underline{H}$=CH), 2.50-1.21 (broad absorption, 3), 1.11 (s, 3, C-4 C$\underline{H}_3$), 1.05 (s, 3, C-4 C$\underline{H}_3$), and 0.96 ppm (d, 3, J=6 Hz, CHC$\underline{H}_3$). Anal. Calcd for $C_9H_{14}O$: C, 78.21; H, 10.21; Found: C, 78.00; H, 9.99.

Further distillation yielded 9.5 g (46%) of a material boiling at 94-100° (2 mm) which was not completely identified but showed infrared and nmr spectral properties consistent with those expected for the

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*Deformylation of the intermediate 6-formyl-4,4,6-trimethyl-2-cyclohexen-1-one is apparently a quite facile process because it occurred under the relatively mild conditions of the work-up step. DeBardeleben (J. F. DeBardeleben, Jr., Ph.D. Dissertation, Georgia Institute of Technology, 1967) made a similar observation for 2-formyl-2,6-dimethyl-4-ethylenedioxycyclohexanone.

O-alkylation product, 6-methoxymethylene-4,4-dimethyl-2-cyclohexen-1-one.

2-Chloro-2-methylcyclohexanone (XVII). 2-Chloro-2-methylcyclohexanone, bp 95-100° (30 mm), (lit. (33) 94-96° (27 mm)) was prepared by the procedure of Warnhoff, Martin, and Johnson (33) in 87% yield. The spectral properties were as follows: ir ($CCl_4$) 1715 $cm^{-1}$ (C=O); nmr ($CCl_4$) $\delta$ 3.33-1.32 (broad absorption, 8) and 1.55 ppm (s, 3, $CClCH_3$).

Reaction of Ketones with Trityl Lithium

General Procedure. A general procedure for preparing lithium enolate mixtures from ketones was followed with variations to allow kinetic or thermodynamic control. In a flame-dried apparatus under positive nitrogen pressure triphenylmethane was dissolved in anhydrous solvent, usually DME or THF, at room temperature, and a solution of phenyl lithium in ether or benzene-ether was added to give a base concentration between 0.02 and 0.20 M. The deep red solution was then stirred for 30-45 min until the complete disappearance of phenyl lithium was indicated by a negative Gilman test (48).

For kinetic lithium enolates the desired temperature for enolate formation was attained. Then about 0.9 equiv of ketone (based on trityl lithium) was added to the solution slowly with a syringe; the solution remained red after the addition. For thermodynamic lithium enolates 1.0 equiv of ketone was introduced, 0.1 to 0.25 equiv was added in excess, and the mixture was equilibrated by stirring at ambient temperature for 18 hrs or at reflux for three hours. The enolate

solutions were trapped with methyl iodide and/or acetic anhydride (49). Acylation was performed by dripping the enolate solution under niteogen into ten equivalents of acetic anhydride over a period of 15-30 min, stirring at room temperature for 30 min, and neutralizing the excess anhydride in a pentane and saturated aqueous sodium bicarbonate mixture (50-75 ml of each per 0.01 mol ketone) at 0-5°. The pentane solution was separated, washed with saturated aqueous sodium bicarbonate, dried over $MgSO_4$ and the product distilled.

Methylations were performed by dripping the enolate solutions under nitrogen into six equivalents (based on lithium enolate) of methyl iodide, or six equivalents of methyl iodide were added rapidly to the enolate solution. After stirring for 30 min, the alkylated product was combined with water and ether (50-75 ml per 0.01 mol ketone). The aqueous phase was separated, saturated with sodium chloride, and extracted three times with ether. The combined ethereal solutions were washed with 3 per cent hydrochloric acid, saturated aqueous sodium bicarbonate, and brine, consecutively.

2-Methylcyclohexanone (IX)--Thermodynamic Mixture. To 9.77 g (0.040 mol) of triphenylmethane dissolved in 125 ml of DME was added 22 ml (0.040 mol) of phenyl lithium in ether (1.8 M). The mixture was stirred for one hour, and 3.97 g (0.036 mol) of IX was titrated into the solution discharging the red color. Then 0.4 g (0.004 mol) of IX was added in excess and the mixture was stirred for 18 hrs at room temperature. The mixture was then dripped into 40 g (0.4 mol) acetic anhydride, and the enol acetates were analyzed. Distillation yielded

3.5 g of material, bp 75-90° (35 mm), consisting of 25 per cent starting material and 75 per cent of a mixture of enol acetates (VPC analysis--10-ft x 0.25-in column, 20 per cent Dow-550 on 80/100 firebrick, 150°, 60 ml/min). The enol acetate mixture,* 1-acetoxy-2-methyl-1-cyclohexene (XVIII) and 1-acetoxy-6-methyl-1-cyclohexene (XIX), could not be separated by VPC; therefore, the composition of the mixture was determined by nmr spectroscopy on a sample collected by VPC. The spectrum of XIX in benzene (15) exhibited a multiplet at $\underline{\delta}$ 5.20 ppm for the vinyl proton and a doublet at $\underline{\delta}$ 0.95 ppm (and also in $CCl_4$ reported here) which were significantly different from absorptions recorded for XVIII and could be used for determination of the composition of the mixture of enol acetates. The mixture consisted of 89 per cent XVIII and 11 per cent XIX; a duplicate run yielded 90 per cent XVIII and 10 per cent XIX.

For a methylation of a thermodynamic lithium enolate 6.42 g (0.025 mol) of triphenylmethane was dissolved in 250 ml of DME and was treated with 0.0219 mol of phenyl lithium (1.8 M in ether). After stirring for one hour the mixture was treated with 2.23 g (0.020 mol) of IX which eliminated the red color. Addition of 0.223 g (0.002 mol) of IX followed, and the mixture was refluxed for three hours and allowed to cool. Finally, 17.0 g (0.12 mol) of methyl iodide was added rapidly, and the alkylated products were analyzed according to the procedure of

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*C. Mannich and V. H. Hanau, *Chem. Ber., 41,* 564 (1908), report a bp of 185-186° for presumably a mixture of XVIII and XIX.

Caine (12). Distillation gave 1.7 g of material, bp 85-95° (40 mm); the mixture consisted of 15 per cent IX, 70 per cent X, 8 per cent cis- and trans-VII, and 7 per cent 2,2,6-trimethylcyclohexanone (XX).

2-Methylcyclohexanone (IX)--Kinetic Mixture. A trityl lithium solution was prepared from 16.0 g (0.062 mol) of triphenylmethane in 310 ml of THF by the addition of 0.05 mol of phenyl lithium (1.4 M in ether). After being stirred for one hour, the red solution was immersed in a Dry Ice and acetone bath for one hour to reach -80°. Next, 4.48 g (0.040 mol) of IX in 10 ml of DME at 0° was added slowly to the trityl lithium solution; stirring of the semi-solid slurry was continued for one hour at -80°. When the mixture warmed to room temperature, one-half was quenched with 20 g (0.20 mol) of acetic anhydride yielding 2.0 g (65 per cent) of XVIII and XIX, bp 85-90° (35 mm). Analysis by nmr spectroscopy of a sample collected by VPC (10-ft x 0.25-in column, 20 per cent Dow-550 on 80/100 firebrick, 150°, 60 ml/min) yielded 92 per cent XIX and 8 per cent XVIII. The remainder was quenched with 17.0 g (0.12 mol) of methyl iodide; distillation of the alkylated mixture yielded 1.51 g of a mixture, bp 85-97° (35 mm), consisting of 5 per cent IX, 71 per cent cis- and trans-VII, 9 per cent X and 15 per cent XX according to the method described previously (12).

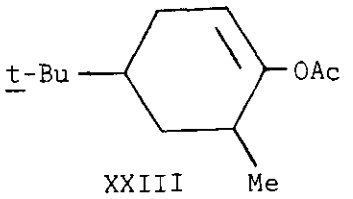
2,2-Dimethylcyclohexanone--Preparation of 1-Acetoxy-6,6-dimethyl-1-cyclohexene (XXI). A solution of trityl lithium was prepared from 150 ml of DME, 3.90 g (0.016 mol) of triphenylmethane and 0.010 mol of phenyl lithium (2.0 M in 70:30 benzene:ether). The red solution became clear on addition of 1.14 g (0.009 mol) of X. The enolate

solution was quenched with acetic anhydride yielding 1.10 g of a mixture, bp 90-98° (25 mm), consisting of 19 per cent X and 81 per cent 1-acetoxy-6,6-dimethyl-1-cyclohexene: ir ($CCl_4$) 1770 (ester C=O) and 1690 $cm^{-1}$ (C=C); nmr ($CCl_4$) $\delta$ 5.17 (t, 1, J=4 Hz, C=C<u>H</u>), 2.16 (m, 2), 2.08 (s, 3, $COCH_3$), 1.61 (m, 4), and 1.01 ppm (s, 6, $C(CH_3)_2$). Anal. Calcd for $C_{10}H_{16}O_2$: C, 71.39; H, 9.59. Found: C, 71.42; H, 9.53.

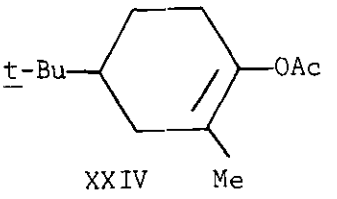
2,6-Dimethylcyclohexanone--Preparation of 1-Acetoxy-2,6-dimethyl-1-cyclohexene (XXII). A trityl lithium solution was prepared from 150 ml of DME, 3.90 g (0.016 mol) of triphenylmethane and 0.010 mol of phenyl lithium (2.0 M in 70:30 benzene:ether). To decolorize the red solution required 1.25 g (0.0099 mol) of VII. The enolate solution was quenched with acetic anhydride yielding 1.47 g of a mixture, bp 110-120° (40 mm), consisting of 10 per cent VII and 90 per cent XXII: ir ($CCl_4$) 1762 (ester C=O) and 1700 $cm^{-1}$ (C=C); nmr ($CCl_4$) $\delta$ 2.95-1.27 (broad absorption, 7), 2.07 (s, 3, $COCH_3$), 1.47 (m, 3, $C=CCH_3$), and 0.95 ppm (d, 3, J=7 Hz, $CHCH_3$). Anal. Calcd for $C_{10}H_{16}O_2$: C, 71.39; H, 9.59. Found: C, 71.45; H, 9.70.

2-Methyl-4-t-butylcyclohexanone (93 Per Cent cis) (XI)--Thermodynamic Mixture. A solution of trityl lithium was prepared from 3.02 g (0.012 mol) of triphenylmethane and 0.0090 mol of phenyl lithium (2.0 M in 70:30 benzene:ether). After being stirred for one hour, the red solution was titrated with 1.30 g (0.0078 mol) of 93 per cent cis-XI. Addition of 0.26 g (0.0016 mol) of XI in excess and heating at reflux for three hours followed. When the mixture cooled, it was quenched with acetic anhydride. The mixture of enol acetates XXIII and

XXIV was separated from excess XI by VPC (5-ft x 0.25-in column, 20 per cent SF-96 on Chromosorb W, 190°, 60 ml/min).




XXIII




XXIV

The composition of the mixture 89.6 per cent XXIV and 10.4 per cent XXIII was determined from the nmr spectrum based essentially on the area of the vinyl absorption in XXIII (multiplet centered at $\underline{\delta}$ 5.20 ppm in $CCl_4$). The infrared spectrum of this mixture displays absorptions at 1750 (ester C=O) and 1710 $cm^{-1}$ (C=C). The nmr spectrum of XXIV could be deduced from the spectrum on the mixture as follows: nmr ($CCl_4$) $\underline{\delta}$ 2.19-1.00 (broad absorption, 7), 2.02 (s, 3, $COC\underline{H}_3$), 1.47 (broadened s, 3, $C{=}CC\underline{H}_3$), and 0.88 ppm (s, 9, $C(C\underline{H}_3)_3$). Anal. Calcd for $C_{13}H_{22}O_2$: C, 74.24; H, 10.55. Found: C, 74.51; H, 10.70. The analysis was performed on the isomeric mixture of enol acetates.

Preparation of the enol acetates of XI by an independent method was performed in an effort to prepare the equilibrium mixture of enol acetates (15). A mixture of 1.01 g (0.006 mol) of XI, 1.2 g (0.014 mol) of isopropenyl acetate and 0.009 g of anhydrous p-toluenesulfonic acid was refluxed overnight. The material boiling from 35-95° was removed, and the residual was stirred with 50 ml of pentane and 50 ml of saturated aqueous sodium bicarbonate at 0-5°. After separation and drying ($MgSO_4$), the pentane layer yielded 1.0 g of material. The

material was identical by VPC analysis (10-ft x 0.25-in column, 20 per cent SE-30 on 60/80 firebrick) to the material prepared by quenching the equilibrium mixture of isomeric lithium enolates of XI. NMR spectral analysis of a sample separated by preparative VPC established the composition of the mixture as 40 per cent XXIII and 60 per cent XXIV.

2-Methyl-4-t-butycyclohexanone (93 per cent cis) (XI)--Kinetic Mixture. The kinetic mixture of lithium enolates of XI was prepared from a trityl lithium solution derived from 2.42 g (0.0099 mol) of triphenylmethane, 50 ml of DME and 0.0075 mol of phenyl lithium (2.0 M in 70:30 benzene:ether) and 1.00 g (0.0060 mol) of XI. The mixture was quenched with acetic anhydride and distilled to yield 0.75 g (60 per cent), bp 70-80° (0.5 mm), of enol acetates containing a minor amount of XI. The composition determined by nmr spectroscopy was 87 per cent XXIII and 13 per cent XXIV.

Reaction of Ketones with Trityl Potassium

General Procedure. Trityl potassium solutions in DME were prepared by the method of House and Kramar from potassium metal, triphenylmethane and 1,3-butadiene (15) in a flame-dried apparatus under nitrogen. For kinetic mixtures of potassium enolates the trityl potassium solution was diluted to give a concentration of about 0.1 M. Then approximately 0.8-0.9 equiv (based on trityl potassium) of ketone was introduced; the solution retained its dark red color at the end of the addition. The mixture was then acylated with acetic anhydride or alkylated with methyl iodide and worked up in a manner analogous to that already described for lithium enolates.

For thermodynamic mixtures of potassium enolates 1.0 equiv (based on trityl base) of ketone was titrated into the solution of trityl potassium. Introduced in excess was 0.1-0.25 equiv of ketone. Equilibrium was carried out by stirring for one hour at room temperature.* The equilibrium mixture was either acylated with acetic anhydride, alkylated with methyl iodide, or in one case, quenched with acetic acid-$\underline{d}_1$ in deuterium oxide (15). The procedure for the deuterium quenching is subsequently described in detail.

2-Methylcyclohexanone (IX)--Thermodynamic Mixture. A solution of trityl potassium was prepared from five milliliters of DME, 1.17 g (0.0046 mol) of triphenylmethane, 0.164 g (0.0042 g-atom) of potassium metal with 1.3 g (0.025 mol) of 1,3-butadiene condensed into the mixture over a 15-min period. After 25 ml of DME was added, 0.350 g (0.00312 mol) of IX was titrated into the red solution barely discharging the red color. Excess IX (0.087 g, 0.0008 mol) was then introduced, and the mixture of potassium enolates was stirred for one hour to allow equilibration. Quenching was performed by adding quickly an acetic acid-$\underline{d}_1$ solution, prepared from 0.212 g (0.021 mol) of acetic anhydride and 16.0 ml of $D_2O$, to the enolate mixture and agitating for 15 min. The aqueous mixture was extracted with three 15-ml portions of ether; the combined ether extracts were dried over anhydrous sodium sulfate. After removal of the solvent *in vacuo*, recovered deuterated IX was collected by VPC (10-ft x 0.25-in column, 20 per cent Dow 550 on

*The rate of equilibration of potassium enolates at room temperature is very rapid (12).

80/100 firebrick, 150°, 60 ml/min). Deuterium analysis showed 4.80 per cent excess deuterium in the recovered IX. The nmr spectrum showed the following in the methyl region: nmr ($CCl_4$) 0.95 (d, 1.49, J=6 Hz, $CHCH_3$) and 0.95 ppm (t, 1.51, J=1 Hz, $CDCH_3$). Accounting for the excess ketone, deuterium incorporation amounted to 72 per cent giving a ratio of IX-2d to IX-6d of 70 to 30*. This agrees well with the values reported by House and Kramar (15) for the equilibrium mixture of potassium enolates of IX in DME and also with the values determined from an acetic anhydride quench performed on an equilibrium mixture of potassium enolates of IX.

2-Methylcyclohexanone (IX)--Kinetic Mixture. A solution of trityl potassium was prepared from 100 ml of DME, 23.4 g (0.092 mol) of triphenylmethane, 3.28 g (0.085 mol) of potassium metal and 10 g (0.19 mol) of 1,3-butadiene. A 300-ml portion of DME was introduced after 30 min of stirring, and 4.48 g (0.040 mol) of IX was dripped into the solution from a syringe. The red mixture was stirred for one hour at room temperature, and then one-half of the solution was quenched with 20 g (0.2 mol) of acetic anhydride. Distillation yielded 1.64 g, bp 90-95° (40 mm), of a mixture containing 68 per cent XIX and 32 per cent XVIII.

For methylation of a kinetic mixture of potassium enolates of IX, a trityl potassium solution was prepared from 4.88 g (0.020 mol) of triphenylmethane, 25 ml of DME, 0.78 g (0.020 mol) of potassium metal and 1.8 g (0.033 mol) of 1,3-butadiene. The red solution was titrated with

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*This computation assumed that all deuterated species were monodeuterated.

a solution of 2.24 g (0.020 mol) of IX in 50 ml of DME until just prior to the endpoint, that is, the dark red color still persisted, but the solution was not opaque. Immediately, 28.4 g (0.20 mol) of methyl iodide was added rapidly transforming the clear red solution into a milky white slurry. Analysis of the alkylated products showed a composition of 12.0 per cent IX, 29.6 per cent cis- and trans-VII, 28.4 per cent X, 27 per cent XX and 4 per cent 2,2,6,6-tetramethylcyclohexanone (XXV) (12). In a duplicate experiment except for dropwise addition of the methyl iodide, the following composition resulted: 7 per cent IX, 11.0 per cent cis- and trans-VII, 50.0 per cent X, 27 per cent XX and 5 per cent XXV.

2-Methyl-4-t-butylcyclohexanone (93 per cent cis) (XI)--Thermodynamic Mixture. A solution of trityl potassium was prepared from 4.0 g (0.016 mol) of triphenylmethane, 20 ml of DME, one milliliter of 1,3-butadiene and 0.48 g (0.012 mol) of potassium. A 125-ml portion of DME was introduced after 30 min of stirring, and 2.00 g (0.0119 mol) of XI in 25 ml of DME was added dropwise. The red color was dissipated after about 90 per cent of the ketone solution had been added. Introduced in excess was 0.36 g (0.0021 mol) of XI; a one-hour period of stirring and acetic anhydride quenching followed. Collection by VPC (5-ft x 0.25-in column, 20 per cent SF-96 on Chromosorb W, 190°, 60 ml/min) and nmr spectral analysis showed 30.5 per cent XXIII and 69.5 per cent XXIV.

2-Methyl-4-t-butycyclohexanone (93 per cent cis) (XI)--Kinetic Mixture. A solution of trityl potassium was prepared from 3.50 g (0.0143 mol) of triphenylmethane, 20 ml of DME, 0.43 g (0.011 mol) of

potassium, and one milliliter of 1,3-butadiene. An additional 55 ml of DME was introduced, and 1.00 g (0.0060 mol) XI was added. The crimson solution was quenched with 10 g (0.10 mol) of acetic anhydride. Distillation produced 0.72 g (57 per cent) of material, bp 60-70° (0.25 mm), consisting of 29.5 per cent XXIV and 70.5 per cent XXIII by nmr spectroscopy.

2-Methyl-4-t-butylcyclohexanone (75 per cent trans)--Kinetic Mixture. A trityl potassium solution was prepared from 2.00 g (0.0082 mol) of triphenylmethane, 15 ml of DME, one milliliter of 1,3-butadiene and 0.281 g (0.0072 mol) of potassium. After increasing the volume with 35 ml of DME, 1.09 g (0.0065 mol) of XI was added; and the deep red solution was stirred for 30 min and quenched with acetic anhydride. Distillation produced 1.05 g (77 per cent) of material, bp 70-75° (0.4 mm), consisting of 97 per cent XXIII of 3 per cent XXIV. The nmr spectrum of XXIII with the methyl group axial may be deduced from the spectrum of this mixture as follows: nmr ($CCl_4$) $\delta$ 5.27 (m, 1, C<u>H</u>=C), 2.19-1.79 (broad absorption, 3), 2.03 (s, 3, COC<u>H</u>$_3$), 1.53 (m, 3), 1.03 (d, 3, J=6 Hz, CHC<u>H</u>$_3$), and 0.90 ppm (s, 9, C(C<u>H</u>$_3$)$_3$).

## Lithium-Liquid Ammonia Reduction of Cyclohexenones

General Procedure for Lithium-Liquid Ammonia Reduction of Cyclohexenones. The reduction of the various $\alpha,\beta$-unsaturated ketones was accomplished in the following manner. A three-necked flask fitted with a mechanical stirrer, a dropping funnel and a Dry Ice condenser was flame dried under a positive nitrogen flow, and the system was maintained under nitrogen throughout the remainder of the experiment. Anhydrous

liquid ammonia (100-200 ml per 0.1 g of lithium used) was introduced into the reaction vessel by distillation from sodium. The liquid ammonia was deemed dry if, after addition of about 0.001 g of lithium wire, the blue color persisted for five minutes. Sufficient freshly cut lithium wire was added to bring the total quantity of lithium to 2.2 g-atom per mole of ketone employed and the solution stirred for 15 min. While stirring was continued, a solution of equimolar quantities of the enone and t-butyl alcohol (in the runs conducted in the absence of a proton donor, the t-butyl alcohol was omitted) in ether was added dropwise over 30 min. Generally the reaction mixture remained blue throughout the addition period. The reaction mixture was stirred for 30 min and excess ammonium chloride was added in small portions with continued stirring. After 30 min the Dry Ice condenser was replaced by a water condenser, and the ammonia was allowed to evaporate. Ether and water were added and the ether layer was separated. The aqueous layer was saturated with sodium chloride and extracted with ether. The combined ethereal solutions were washed with 5 per cent hydrochloric acid, saturated aqueous sodium chloride, and dried over anhydrous magnesium sulfate. The ether was removed under reduced pressure, and the residue was either distilled and analyzed by VPC or analyzed directly by VPC using an internal standard.

Reductions of 2-Methyl-2-cyclohexen-1-one (XII). Using 0.50 g (0.072 g-atom) of lithium in 500 ml of liquid ammonia, 3.63 g (0.033 mol) of XII and 2.44 g (0.033 mol) of t-butyl alcohol in 50 ml of ether, and 5.25 g (0.099 mol) of ammonium chloride, 1.82 g (50 per cent) of

material, bp 78-81° (30 mm), was obtained. The product was shown to be pure by VPC analysis (10-ft x 0.25-in column, 20 per cent SE-30 on 60/80 firebrick), and it showed VPC behavior and spectral properties identical with those of 2-methylcyclohexanone. In a run using 0.175 g (0.025 g-atom) of lithium in 200 ml of liquid ammonia, 1.10 g (0.01 mol) of XII in 50 ml of ether, and 1.65 g (0.030 mol) of ammonium chloride, the recovered mixture of ketones showed calculated yields (by VPC using m-xylene as an internal standard) of 47 per cent IX and 15 per cent XII.

Reduction of 4,4,6-Trimethyl-2-cyclohexen-1-one (XVI). Using 0.137 g (0.020 g-atom) of lithium in 250 ml of liquid ammonia, 1.08 g (0.008 mol) of XVI and 0.579 g (0.008 mol) of t-butyl alcohol in 50 ml of ether, and 1.66 g (0.031 mol) of ammonium chloride, 2,4,4-trimethylcyclohexanone (XXVI), bp 83-87° (23 mm) (lit. (51) bp 87-89° (30 mm)), 2,4-dinitrophenylhydrazone, mp 149-150° (lit. (52) mp 150-151°), ir (film) 1720 $cm^{-1}$ (C=O), and nmr ($CCl_4$) $\delta$ 2.89-1.55 (broad absorption, 7), 1.22 (s, 3, C-4 $CH_3$), 1.00 (s, 3, C-4 $CH_3$), and 0.90 ppm (d, 3, J=6 Hz, $CHCH_3$), was obtained. The calculated yield by VPC (10-ft x 0.25-in column, 20 per cent SE-30 on 60/80 firebrick) using m-xylene as an internal standard was 80 per cent.

Reductions of 3-Methyl-2-cyclohexen-1-one (XIV). Using 0.320 g (0.046 g-atom) of lithium in 500 ml of liquid ammonia, 2.00 g (0.018 mol) of XIV and 1.36 g (0.018 mol) of t-butyl alcohol in 50 ml of ether, and 4.00 g (0.075 mol) of ammonium chloride, 1.24 g (62 per cent) of material, bp 85-95° (40 mm), was obtained. This product was

shown to be pure by VPC (5-ft x 0.25-in column, 15 per cent SF-96 on Chromosorb W), and it showed VPC and spectral properties identical with those of an authentic sample of 3-methylcyclohexanone (XXVII).

Using 0.0470 g (0.0068 mol) of lithium in 100 ml of liquid ammonia, 0.297 g (0.0027 mol) of XIV in 50 ml of ether, and 0.570 g (0.011 mol) of ammonium chloride, a product showing only one component by VPC analysis (5-ft x 0.25-in, 15 per cent SF-96 on Chromosorb W) and having a retention time identical with that of XXVII was obtained. The calculated yield by VPC analysis employing m-xylene as an internal standard was 66 per cent.

Reduction of 7β-Isopropyl-10α-methyl-$\Delta^{1(9)}$-octalone-2 (XV). Using 0.462 g (0.066 g-atom) of lithium in 1000 ml of liquid ammonia, 6.18 g (0.030 mol) of XV and 2.22 g (0.030 mol) of t-butyl alcohol in 200 ml of ether and 6.42 g (0.12 mol) of ammonium chloride, 4.19 g (67 per cent) of trans-7β-isopropyl-10α-methyl-2-decalone, bp 115-122° (0.2 mm), mp 101-103° (lit. (44) 103-105°), ir ($CCl_4$) 1720 $cm^{-1}$ (C=O); nmr ($CCl_4$) 2.50-1.10 (broad absorption, 15), 1.05 (s, 3, $CCH_3$), and 0.89 ppm (d, 6, J=6 Hz, $CH(CH_3)_2$). The material only showed one component by VPC analysis on several columns indicating that the trans-isomer was present virtually exclusively.

Reduction-Methylation of Cyclohexenones and α-Halocyclohexanones

General Procedure for the Reduction-Methylation of Cyclohexenone Derivatives. The enones, XII, XIII, XIV, and XVI as well as 2-chloro-2-methylcyclohexanone were converted into lithium enolates by a procedure identical with that described for the reduction runs. A solution

of lithium in liquid ammonia was prepared by addition of freshly cut lithium wire (2.2 g-atoms/mol of enone used) to anhydrous liquid ammonia and stirred for 15 min. The enone, dissolved in anhydrous ether, was then added dropwise with stirring over 30 min to this solution. (Unless otherwise specified, one equivalent of anhydrous t-butyl alcohol was dissolved in the ether solution of the enone. Whenever water was used as the proton donor, DME was employed as the solvent at this stage). The reaction mixture was stirred for 30 min and diluted with an equal volume of anhydrous ether. For the alkylation step, an excess of methyl iodide dissolved in ether was added dropwise over 30-40 min. After the mixture had been stirred for an additional 30-min period, the liquid ammonia was allowed to evaporate. The reaction mixture was worked up in a manner similar to that described for the reduction runs.

Reduction-Methylation of 2-Methyl-2-cyclohexen-1-one (XII). Employing 0.958 g (0.138 g-atom) of lithium in 500 ml of liquid ammonia, 6.60 g (0.060 mol) of XII and 4.44 g (0.060 mol) of t-butyl alcohol in 50 ml of ether, and 400 ml of ether followed by 42.6 g (0.300 mol) of methyl iodide in 50 ml of ether, 3.70 g (49 per cent) of a mixture of ketones, bp 80-85° (35 mm), was obtained. Analysis of the mixture by VPC (10-ft x 0.25-in column, 20 per cent SE-30 on 60/80 firebrick) and nmr spectroscopy as described previously (12) showed that it contained 80 per cent 2,2-dimethylcyclohexanone (X), 18 per cent 2,2,6-trimethylcyclohexanone (XX), and 2 per cent 2-methylcyclohexanone (IX). No 2,6-dimethylcyclohexanone (VII) was detected. A mixture of ketones of identical composition was obtained from a duplicate run on XII.

In another experiment employing 0.525 g (0.075 g-atom) of lithium in 500 ml of liquid ammonia, 3.30 g (0.030 mol) of XII and 0.540 g (0.030 mol) of water in 50 ml of DME, and 400 ml of ether followed by 26.5 g (0.18 mol) of methyl iodide in 50 ml of ether, a mixture of ketones consisting of 96 per cent X, 2 per cent XX, and 2 per cent IX was obtained. The calculated yield by VPC (10-ft x 0.25-in column, 20 per cent SE-30 on 60/80 firebrick) using m-xylene as an internal standard was 63 per cent in this run.

A reduction-methylation was performed on XII in the absence of a proton donor by employing 0.525 g (0.075 g-atom) of lithium in 500 ml of liquid ammonia, 3.12 g (0.028 mol) of XII in 50 ml of ether and 400 ml of ether followed by 26.5 g (0.180 mol) of methyl iodide in 50 ml of ether. A 2.80-g quantity of a mixture of ketones was obtained, and VPC analysis (10-ft x 0.25-in column, 20 per cent SE-30 on 60/80 firebrick) of the mixture revealed the presence of two peaks in a 95:5 ratio. The minor component of the mixture had a retention time identical with that of the trimethyl ketone XX. The major peak was collected by preparative VPC and integration of the nmr spectrum of this mixture revealed that it contained 60 per cent X and 40 per cent unreacted enone XII. No unsaturated methylation products were observed. The product yields were not determined in this run.

Reduction-Methylation of 6-Methyl-2-cyclohexen-1-one (XIII). Employing 0.483 g (0.069 g-atom) of lithium in 500 ml of liquid ammonia, 3.30 g (0.030 mol) of XIII and 2.22 g (0.030 mol) of t-butyl alcohol in 50 ml of ether, and 400 ml of ether followed by 21.3 g (0.150 mol) of

methyl iodide in 50 ml of ether, 1.50 g (42 per cent) of a mixture of ketones, bp 75-78° (20 mm), was obtained. Analysis of the mixture as described above showed that it contained 86 per cent of the equilibrium mixture of cis- and trans-2,6-dimethylcyclohexanone (VII), 2 per cent 2,2,6-trimethylcyclohexanone (XX) and 12 per cent 2-methylcyclohexanone (IX). No 2,2-dimethylcyclohexanone (X) was detected.

The effectiveness of sodium in the reduction-methylation was checked by employing 1.72 g (0.075 mol) of sodium in 500 ml of liquid ammonia, 3.30 g (0.030 mol) of XIII and 2.22 g (0.030 mol) t-butyl alcohol in 50 ml of ether, and 400 ml of ether followed by 21.3 g (0.150 mol) of methyl iodide in 50 ml of ether. 1.92 g of a mixture of four products was obtained. The crude product showed a strong hydroxyl absorption in the infrared spectrum. The major product, collected by preparative VPC (10-ft x 0.25-in column, 20 per cent SE-30 on 60/80 firebrick), was 2,2,6,6-tetramethylcyclohexanone: ir (film)* 1692 (C=O), 1370 and 1350 $cm^{-1}$ ($C(CH_3)_2$); nmr ($CCl_4$) $\delta$ 1.09 (s, 12) and 1.69 ppm (m, 6). The preponderant peak of the minor products was an alcohol with no significant infrared absorptions in the 5.0-6.0 $\mu$ region. The other two peaks were not identified.

Reduction-Methylation of 4,4,6-Trimethyl-2-cyclohexen-1-one (XVI). Employing 0.268 g (0.038 g-atom) of lithium in 250 ml of liquid ammonia, 2.07 g (0.015 mol) of XVI and 1.10 g (0.015 mol) of t-butyl alcohol in

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*This spectrum also showed a significant hydroxyl absorption at 3460 $cm^{-1}$ indicating that the sample was not completely pure.

50 ml of ether, and 150 ml of ether followed by 10.7 g (0.075 mol) of methyl iodide in 50 ml of ether, 1.40 g (60 per cent) of a mixture of ketones, bp 57-59° (3.5 mm), was obtained. VPC analysis (10-ft x 0.25-in column, 20 per cent SE-30 on 60/80 firebrick and 10-ft x 0.25-in column, 15 per cent 4-MNP on acid washed firebrick) showed that it contained 95 per cent 2,4,4,6-tetramethylcyclohexanone (XXVIII) and 5 per cent 2,4,4-trimethylcyclohexanone (XXVI). No 2,2,4,4-tetramethylcyclohexanone* (XXIX) or pentamethylcyclohexanone was detected. A sample of XXVIII collected by preparative VPC (10-ft x 0.25-in column, 20 per cent SE-30 on 60/80 firebrick) and refluxed for ten hours with 15 per cent hydrochloric acid to insure formation of the thermodynamic mixture of cis and trans isomers. It showed the following spectral properties: ir ($CCl_4$) 1710 $cm^{-1}$ (C=0); nmr** ($CCl_4$) $\delta$ 2.25-1.42 (broad absorption, 6), 1.27 (s, 3, C-4 $CH_3$), 0.97 (s, 3, C-4 $CH_3$), and 0.91 ppm (d, 6, J=7 Hz, $CHCH_3$). Anal. Calcd for $C_{10}H_{18}O$: C, 77.86; H, 11.75. Found: C, 77.87; H, 11.96.

Reduction-Methylation of 3-Methyl-2-cyclohexen-1-one (XIV). Using 0.928 g (0.132 g-atom) of lithium in 500 ml of liquid ammonia,

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*The 4-MNP column separated 2,4,4,6-tetramethylcyclohexanone and an authentic sample of 2,2,4,4-tetramethylcyclohexanone, supplied by Mr. W. J. Powers, III.

**An experiment performed by Mr. T. Mitt confirmed the nmr assignments which were ambiguous because the low-field peak of the doublet at 0.91 ppm overlapped with the singlet at 0.97 ppm. On refluxing XXVIII with deuterium oxide and potassium carbonate, the intensity of the peaks at 0.87 and 0.97 ppm was reduced, and a triplet (J=0.6 Hz) at 0.91 ppm characteristic of methyl groups split by deuterium appeared.

5.83 g (0.053 mol) of XIV and 3.92 g (0.053 mol) of t-butyl alcohol, and 400 ml of ether followed by 32.3 g (0.23 mol) of methyl iodide in 50 ml of ether, 3.60 g (54 per cent) of a mixture of ketones, bp 85-95° (40 mm), was obtained. VPC (10-ft x 0.25-in column, 20 per cent SE-30 on 60/80 firebrick) analysis showed that this mixture contained two components in an 87:13 ratio. The major component of the mixture was collected by VPC. Its nmr spectrum showed absorptions expected for 2,3-dimethylcyclohexanone (XXX), that is, three peaks at 0.91, 1.03, and 1.10 ppm totaling six protons and resulting from overlapping doublets for the C-2 and C-3 methyl groups and at 1.25-2.5 ppm for the remaining eight protons. The minor component of the mixture was not positively identified, but, since its VPC retention time did not correspond with that of either XIV or XXVII and since the infrared spectrum of the crude reaction mixture showed no hydroxylic absorption, it was assumed to be either 2,3,6-trimethylcyclohexanone (XXXI) or 2,2,3-trimethylcyclohexanone (XXXII) or a mixture of these.

In order to establish definitely that XXX was the only monoalkylation product produced in the reaction, the crude ketone mixture was converted to the semicarbazone, mp 185-195° (lit. (53) mp 205° for the semicarbazone of XXX), and this derivative was subjected to Wolff-Kishner reduction according to the method of Claudon and co-workers (53). VPC analysis (10-ft x 0.25-in column, 20 per cent Dow-550 on 80/100 firebrick) of the mixture of hydrocarbons showed that it contained two components in a 85:15 ratio. The major component showed a

retention time identical with that of trans-1.2-dimethylcyclohexane*. In addition, a sample of the major component was collected by VPC, and it showed an nmr spectrum identical with that reported by Muller and Tosch (54) for trans-1,2-dimethylcyclohexane. The minor component had a longer retention time than that of any of the isomeric dimethylcyclohexanes.

Reduction-Methylation of 2-Chloro-2-methylcyclohexanone (XVII). Employing 0.35 g (0.050 mol) of lithium in 500 ml of liquid ammonia, 2.92 g (0.020 mol) of XVII in 50 ml of ether, and 400 ml of ether followed by 17.0 g (0.12 mol) of methyl iodide, a mixture of ketones consisting of 98 per cent X and 2 per cent IX was obtained in 85 per cent yield by VPC (10-ft x 0.25-in column, 20 per cent SE-30 on 60/80 firebrick) using m-xylene as an internal standard.

Another experiment employing 3.60 g (0.52 mol) of lithium in 500 ml of liquid ammonia, 30.0 g (0.21 mol) of XVII in 100 ml of ether (90-min period of addition), and 250 ml of ether followed by 117 g (0.82 mol) of methyl iodide in 150 ml of ether was performed. A mixture of ketones containing approximately 50 per cent IX and 50 per cent X was obtained.

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*Authentic samples of both cis- and trans-1,2-dimethylcyclohexane and cis- and trans-1,4-dimethylcyclohexane were separated on the Dow-550 column. Dr. J. A. Stanfield kindly furnished authentic samples of these hydrocarbons.

## Kinetics of Alkylation of Cyclohexanones

### Preparation of Reagents

The cyclohexanone derivatives, IX, X, VII, cis-XI, and cyclohexanone (XXXIII), used in kinetic studies, were distilled and stored over anhydrous magnesium sulfate in dark containers. DME solvent was prepared as described earlier; in one case N,N-dimethylformamide was used as an additive and was purified by the method of Fieser (55). Methyl iodide, ethyl iodide, and allyl bromide were stored over anhydrous calcium chloride and distilled immediately prior to use. Methyl p-toluenesulfonate was used directly; n-butyl bromide was dried over calcium chloride, distilled, and stored as a solution in DME in a container protected from light.

### General Procedure for Kinetic Studies with Lithium Enolates

The following routine was followed in virtually all determinations of the rate of alkylation of the lithium enolates. In a flame-dried apparatus purged with nitrogen under positive nitrogen pressure 200 ml (250 ml in some cases) of previously thermostated DME* was added to approximately 1.25 equiv of triphenylmethane based on the desired trityl base concentration. Next, enough phenyl lithium (about 2.0 M in ether

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*The previous thermostating was not possible for runs at 0°, because water easily condensed onto the cannula of the syringe used for transferring the solvent, and the rate of reaction of phenyl lithium with triphenylmethane was reduced greatly. Therefore, 200 or 250 ml of DME were measured into the reaction vessel at ambient temperature and a correction factor for volume (0.958) (estimated from data given in the Merck Index, 7th ed., 1960, p. 367) was used to account for the increase in the density of DME at 0°.

or in 70:30 benzene:ether) (usually more than three but less than 15 ml) was added to the DME solution to yield the desired trityl lithium concentration, and the mixture was stirred for one hour. In every case the absence of phenyl lithium was demonstrated by a negative Gilman (48) test. For ketones that did not produce mixtures of isomeric enolates, for example, X, VII, and XXXIII, and for kinetic mixtures of lithium enolates of unsymmetrical ketones, such as IX and cis-XI, the ketones were titrated into the trityl lithium solutions slowly from a syringe until the deep red color was discharged. A 10 per cent excess of ketone was introduced to eliminate catalysis by free ketone as a variable (19) between the kinetic type of enolate mixtures and the equilibrium type of enolate mixtures which required excess ketone for equilibration. For thermodynamic mixtures of lithium enolates of IX and cis-XI, a three-hour period of refluxing was included for equilibration.

Finally, the reaction mixtures which required thermostating (including all runs at 0° and all equilibrium mixtures of enolates) were brought to the desired reaction temperature of vigorous stirring under nitrogen in a constant temperature bath. (The temperatures used were 0°, 25.10° ± 0.01°, and 29.95° ± 0.05°.) When thermal equilibrium was established the initial enolate concentration was determined by quenching an aliquot (usually 10 ml) in water and titrating the base produced with standard (0.03-0.04 M) perchloric acid solution using a phenolphthalein indicator. This quantity gives the total

base concentration. To find the extraneous base* concentration an aliquot (usually 10 ml) is reacted with excess (5 ml) methyl iodide and then poured into water. Titration of this basic solution gives the extraneous or non-enolate base, because methyl iodide reacts much faster with lithium enolates than with non-enolate bases (13). Subtracting the two titrations yielded the initial lithium enolate concentration. The previously thermostated alkylating agent was added neat in the case of ethyl iodide or in a standard DME solution with the other alkylating agents. Additivity of volumes was assumed at this stage and initial concentration determinations were adjusted accordingly. The reaction was followed by removing 10-ml aliquots under positive nitrogen flow, quenching with water, and titrating with standard acid.

General Procedure for Kinetic Studies with Potassium Enolates

The following routine was executed in almost all determinations of the rate of alkylation of potassium enolates of IX, X, and VII with n-butyl bromide. In a flame-dried apparatus under positive nitrogen pressure a solution of trityl potassium was prepared in a small amount of previously thermostated DME (one milliliter of DME per 0.001 g-atom of potassium used) containing 1.25 equiv of triphenylmethane based on the desired trityl potassium concentration by the addition of potassium metal and 1,3-butadiene as described earlier. After formation of trityl

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*Extraneous base is always present when phenyl lithium is used in solution because the organometallic reagent cleaves ether slowly. The bulk of the extraneous base is lithium ethoxide with some lithium hydroxide which could result from traces of water inadvertently introduced into the system during transfers.

potassium was complete, enough previously thermostated DME was added to bring the volume to 200 ml. Because the solution was already at constant temperature, the initial enolate concentration was determined in the fashion described for lithium enolates.* An amount of n-butyl bromide (10 ml of a DME solution) commensurate with the desired concentration of alkylating agent was introduced, and the reaction rate was followed by removal of aliquots at various times, quenching in water and titrating with standard perchloric acid.

Product Studies Related to Kinetic Runs

For several runs the amount of C-alkylation was determined at a certain percentage of reaction indicated by the titration method. The procedure involved quenching a large aliquot of the reaction mixture in water, isolating the ketones by ether extraction, and analyzing the products by VPC. The material producing the first peak after starting material was collected by VPC, calibrated against the starting material under identical conditions, and used to determine the extent of reaction. In certain cases a cursory spectral examination was given to the collected products to establish qualitatively their respective identity as monoalkylated products. The reactions followed in this manner are given in Table 1 on the following page, and other pertinent data are presented subsequently.

In runs E and F no polyalkylation was detected even though the method used was shown to be sensitive as low as 2 per cent.

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*Usually only minor amounts of extraneous base were present in trityl potassium solutions.

Table 1. Amount of C-Alkylation Observed in Kinetic Runs

| Run No. | Ketone | Metal | Type of Enolate | (RX)[a] | Percentage Reaction by VPC[b] | Percentage Reaction by Titration | Temp |
|---|---|---|---|---|---|---|---|
| A | VII | Li | - | EtI | 39.6 | 40.5 | 0°C |
| B | X | Li | - | EtI | 27.8 | 27.7 | 0° |
| C | VII | K | - | n-BuBr | 37.7 | 43.2 | 30° |
| D | X | K | - | n-BuBr | 33.3 | 37.2 | 30° |
| E | IX | Li | Kin[d] | MeOTs[e] | 16.0[f] | 20.0 | 25° |
| F | IX | Li | Eqm[g] | MeOTs | 16.0[f] | 20.0 | 25° |
| G | IX | Li | Kin | $C_3H_5Br$[h] | 18.0 | 18.0 | 0° |
| H | IX | Li | Eqm | $C_3H_5Br$ | 16.4 | 18.2 | 0° |
| J | IX | Li | Kin | EtI | 20.0 | 20.0 | 0° |
| K | IX | Li | Eqm | EtI | 19.0 | 20.0 | 0° |

[a] General alkylating agent.

[b] 10-ft x 0.25-in column, 20 per cent SE-30 on 60/80 firebrick for Runs A, B, E, F, J and K; 3-ft x 0.25-in column, 20 per cent SE-30 on 60/80 firebrick for all other runs.

[c] Temperature maintained by a crushed ice/water mixture.

[d] Kinetic mixture.

[e] Methyl p-toluenesulfonate.

[f] The low values found here are due either to O-alkylation or competing reaction with extraneous base (13).

[g] Equilibrium or thermodynamic mixture.

[h] Allyl bromide.

Runs J and K showed that 3-4 per cent of the C-alkylation was polyalkylated material based on the area of the next peak after the monoalkyl product by VPC, although the material producing this peak was not completely identified. Runs A and B showed no polyalkylation, and Runs C and D could not be reliably checked; therefore, in the case of C (and D) polyalkylation was probably responsible for the extent of reaction by VPC being only 90 per cent of that by titration. The only alkylating agent which showed significant polyalkylation was allyl bromide which yielded 6.5 per cent of the C-alkylated ketones as diallyl material for Run H and 8.0 per cent for Run G. For every case followed C-alkylation was the predominant reaction path, and with the exception of the metal enolates of IX with methyl p-toluenesulfonate mono-C-alkylation was virtually quantitative. Quantitative mono-C-alkylation was tacitly assumed in all cases not followed.

The pertinent data for the products were as follows: Run A--ir ($CCl_4$) 1705 $cm^{-1}$ (C=O); nmr ($CCl_4$) methyl:methylene protons 1:1, very complicated methyl region since four isomers are possible; mass spectrum 70 eV m/e (rel intensity) 154 (21); Run B--ir ($CCl_4$) 1708 $cm^{-1}$ (C=O); nmr ($CCl_4$) one methyl/one methylene, with singlets at 1.00 and 1.17 ppm for the two α-methyl groups. For Run C the infrared spectrum of the product showed an absorption at 1700 $cm^{-1}$ (C=O) and the mass spectrum showed a peak at m/e (rel intensity) 182 (36). The product from Run D exhibited the same VPC retention time as for Run C and also gave a yellow 2,4-dinitrophenylhydrazone. Of course, the products from Runs E and F were completely characterized by the procedure of Caine (12).

The product from Run H showed the following: nmr ($CCl_4$) $\delta$ 6.1-4.8 (resembles a system of three interacting nuclei (56), 3, $C\underline{H}=C\underline{H}_2$), 2.23 (m, 4), 1.70 (m, 6), and 1.03 ppm (s, 3, $CC\underline{H}_3$). This spectrum is consistent with the structure of 2-methyl-2-allylcyclohexanone, which should have been the major product (with about 10 per cent of 2-methyl-6-allylcyclohexanone). The product from Run G showed the same retention time as that from Run H by VPC, and an nmr spectrum showing the following integration vinyl: $CH_2$: $CH_3$ equal to 3:10:3. The spectrum was complicated by the presence of a mixture of position and geometric isomers. Finally the nmr spectrum for the product from Run J indicates 5 methylene:3 methyl protons. The methyl region is very complicated on account of mixtures of position and geometric isomers. The retention time by VPC of the product from Run K was identical to that from Run J. No further characterization* was attempted because of the complexity of the product mixtures.

Mathematical Procedures

In the alkylations of cyclohexanone and 2-methylcyclohexanone with a variety of alkylating agents, meaningful rate constants were not obtained. In these cases the average initial rate was secured by determining the time for 20 per cent reaction from a plot of concentration versus time and dividing it into the corresponding change in concentrations. All first order rate constants, determined when the data warranted, were derived from a least squares (57) plot of log

*Mass spectra were run on the samples that were still available when the M-66 became available.

concentration versus time; the standard deviation of the slope was also determined. All second order rate constants (58) were calculated according to Equation 3, where k is the second order rate constant in l/(mol x sec),

$$k = \frac{2.303}{(b-a)t} \log \frac{a(b-x)}{b(a-x)} \qquad (3)$$

a is the initial concentration of the enolate in mol/l, b is the initial concentration of the alkylating agent in mol/l, x is the amount of enolate (or alkylating agent) consumed in mol/l, and t is the time in sec. Fractional orders when applicable were determined by the method of initial rates (59). Activation parameters were calculated from rates at 0° and 29.95° using $\underline{\Delta}H^{\neq} = E_a - RT$ where $E_a = 2.303RT_2T_1(\log k_2 - \log k_1)/(T_2-T_1)$, $\underline{\Delta}F^{\neq} = -2.303RT \log (hk_r^{25°}/kT)$, and $\underline{\Delta}S^{\neq} = (\underline{\Delta}H^{\neq} - \underline{\Delta}F^{\neq})/T$ where the symbols have their usual significance (60).

Because rates of alkylation were determined on isomeric mixtures of enolates in some cases, the following procedure was used to separate the individual rate of each isomer.

$$\underline{v}_1X_1 + \underline{v}_2X_2 = \underline{v}_{KIN} \qquad (4)$$

$$\underline{v}_1X_1 + \underline{v}_2X_2 = \underline{v}_{EQM}$$

The number $\underline{v}_1$, represents the initial rate (or rate constant) of isomer 1; $X_1$ represents the proportion of isomer 1 in the mixture; $\underline{v}_2$ and $X_2$

represent analogous quantities for isomer 2; $\underline{v}_{KIN}$ represents the initial rate (or rate constant) for the kinetic mixture of metal enolates; $\underline{v}_{EQM}$ represents the corresponding property of the thermodynamic mixture of metal enolates. Equation 4 was solved to obtain $\underline{v}_1$ and $\underline{v}_2$.

Special Experiments Required by Kinetic Runs

Determination of Enolate Equilibration for Kinetic Mixtures of Metal Enolates During the Early Portion of the Alkylation. An enolate solution was prepared at 25.10° from 250 ml of DME, 6.42 g (0.0263 mol) of triphenylmethane, 0.0175 mol of phenyl lithium, 1.95 g (0.0175 mol) of IX and 0.195 g (0.0018 mol) of IX in excess. Then 2.2900 g (0.01213 mol) of methyl p-toluenesulfonate was added quickly, and the mixture was stirred at 25.10° for 30 min (about 30-35 per cent reaction based on previous runs at similar concentration). The mixture was poured into 200 ml of water/200 ml of ether. The aqueous portion was removed, saturated with sodium chloride, and extracted with ether. The combined ether extracts were washed with saturated aqueous sodium chloride and dried over anhydrous sodium sulfate. VPC analysis (10-ft x 0.25-in column, 20 per cent SE-30 on 60/80 firebrick) showed no XX. The composition of the dimethylcyclohexanones was as follows: 19 per cent X and 81 per cent cis- and trans-VII. Thus, no significant equilibration occurred during the early portion of the alkylation reaction.

Solvent Shell-Equatorial Methyl Interaction in the Lithium Enolate of 2,6-Dimethylcyclohexanone (VII). An enolate solution was prepared from 150 ml of DME, 6.42 g (0.026 mol) of triphenylmethane, 0.011 mol phenyl lithium (1.6 M solution in ether), and 1.40 g (0.011

mol) of VII. After 30 min of stirring the colorless enolate solution was added very slowly to a vigorously stirred solution of 150 ml of 50 per cent acetic acid at 0°. This mixture was transferred to an ice-cold mixture of 100 ml of $H_2O$ and 200 ml of ether, and the ether layer was removed. The aqueous layer was saturated with sodium chloride and extracted with three 100-ml portions of ether. All ethereal solutions were combined with 200 ml of ice-cold saturated aqueous sodium bicarbonate solution and completely neutralized at 0° by addition of solid sodium bicarbonate. Separation of the ethereal extracts, washing with saturated aqueous sodium bicarbonate and brine, and drying over anhydrous sodium sulfate followed. VPC (silicone SE-30 column, F & M instrument) separated the cis and trans isomers yielding 43.9 per cent trans- and 56.1 per cent cis-VII*. Taking 0.9 kcal/mol (61) to be the 1,3-methyl-hydrogen, quasiaxial-axial interaction, the quasiequatorial methyl-solvent shell interaction in DME was calculated to be 0.75 kcal/mol.

Relative Stability of the Metal Enolates of Mixtures of Ketones. A lithium enolate solution was prepared from 3.50 g (0.0143 mol) of triphenylmethane, 150 ml of DME, 0.0114 mol of phenyl lithium (2.0 M in 70:30 benzene:ether), 1.44 g (0.0114 mol) of a 1:1 mixture of VII and X, and 1.59 g (0.0126 mol) of the same mixture in excess. A three-hour period at reflux to allow equilibration and an acetic anhydride quench followed. VPC analysis (10-ft x 0.25-in column, 20 per cent

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*The starting material was 92 per cent cis- and 8 per cent trans-2,6-dimethylcyclohexanone.

Dow-550 on 80/100 firebrick) demonstrated that the mixture contained 70.4 per cent XXII and 29.6 per cent XXI. A duplicate experiment resulted in a mixture containing 67.7 per cent XXII and 32.3 per cent XXI.

Lithium enolates from IX and XI were also equilibrated. A solution of lithium enolates were prepared from 5.39 g (0.0225 mol) of triphenylmethane, 125 ml of DME, 0.018 mol of phenyl lithium (2.0 M in 70:30 benzene:ether), 2.52 g (0.018 mol) of a 1:1 mixture of IX and XI, and 2.77 g (0.020 mol) of the same mixture in excess. A three-hour period at reflux and an acetic anhydride quench followed. By VPC analysis (10-ft x 0.25-in column, 20 per cent SE-30 on 60/80 firebrick) the mixture of enol acetates consisted of 59.1 per cent of enol acetates from XI and 40.9 per cent of enol acetates from IX.

Lithium enolates from a mixture of VII and XI were also equilibrated. A lithium enolate solution was prepared in a manner like the one just described except that 2.71 g (0.0184 mol) of a 1:1 mixture of VII and XI and 2.98 g (0.020 mol) of the same mixture in excess were used to form the lithium enolates. Equilibration, quenching, and VPC analysis (10-ft x 0.25-in column, 20 per cent SE-30 on 60/80 firebrick) of the enol acetates produced showed that the mixture of enol acetates consisted of 81.8 per cent of enol acetates from XI and 18.2 per cent of XXII.

A potassium enolate solution was prepared from a trityl potassium solution derived from 3.50 g (0.0143 mol) of triphenylmethane, 20 ml of DME, two milliliters of 1,3-butadiene, and 0.52 g (0.0133 mol) of

potassium, 180 ml of additional DME, 1.05 g (0.0084 mol) of a 1:1 mixture of VII and X, and 1.17 g (0.0093 mol) of the same mixture in excess. After stirring for one hour at room temperature, quenching with acetic anhydride was performed. VPC analysis (10-ft x 0.25-in column, 20 per cent Dow-550 on 80/100 firebrick) showed that the mixture contained 54.2 per cent XXI and 45.8 per cent XXII. A duplicate experiment resulted in an equilibrated composition of 55.4 per cent XXI and 44.6 per cent XXII.

## Stereochemistry of Alkylation

### Methylation of the Lithium Enolate of 4-t-Butylcyclohexanone

A solution of trityl lithium was prepared as described earlier from 50 ml of DME, 3.05 g (0.0125 mol) of triphenylmethane, and 0.0100 mol of phenyl lithium (2.0 M in 70:30 benzene:ether). Then a solution of 1.54 g (0.0100 mol) of 4-t-butylcyclohexanone in 25 ml of DME was added slowly until the red color was dissipated. After a 30-min period for stirring, 8.52 g (0.060 mol) of methyl iodide was added rapidly. After 30 min one-half of the solution was added to a stirred mixture of 30 ml of water and 30 ml of ether; ether extraction and washing of the combined extracts with 2 per cent hydrochloric acid, saturated aqueous sodium bicarbonate, and brine followed. VPC analysis (10-ft x 0.25-in column, 15 per cent 4-MNP on acid washed firebrick) showed the following composition: 10 per cent 4-t-butylcyclohexanone, 75 per cent cis- and trans-XI and 15 per cent dimethyl-4-t-butylcyclohexanones. The ratio of cis-XI to trans-XI was 55 to 45. Two other experiments run under

similar conditions gave a ratio of cis-XI to trans-XI within 5 per cent of that reported above.

In order to obviate arguments concerning equilibration of the alkylated products during work-up, an alkylated sample of 4-t-butylcyclohexanone prepared from 1.52 g (0.0062 mol) of triphenylmethane, 75 ml of dry DME, 0.0050 mol of phenyl lithium, 0.77 g (0.0050 mol) of 4-t-butylcyclohexanone and 4.2 g (0.030 mol) of methyl iodide was worked up in deuterium oxide in the manner for alkylations described earlier. A sample of XI collected by VPC (10-ft x 0.25-in column, 20 per cent SE-30 on 60/80 firebrick) showed only 0.08 per cent excess deuterium; therefore, equilibration during work-up was negligible.

Methylation of the Equilibrium Mixture of Lithium Enolates from cis-2-Methyl-4-t-butylcyclohexanone (XI)

To a trityl lithium solution derived from 50 ml of DME, 1.52 g (0.0062 mol) of triphenylmethane and 0.0050 mol of phenyl lithium was added 0.77 g (0.0050 mol) of 93 per cent cis-XI and 0.192 g (0.00125 mol) of 93 per cent cis-XI in excess. After equilibration and cooling, 4.2 g (0.030 mol) of methyl iodide was added rapidly. Distillation yielded 0.62 g of material, bp 78-90° (3.5 mm), of the following composition: 28.4 per cent XI, 53.0 per cent 2,2-dimethyl-4-t-butylcyclohexanone (XXXIV), 5.2 per cent 2,6-dimethyl-4-t-butylcyclohexanone (XXXV), and 12.4 per cent 2,2,6-trimethyl-4-t-butylcyclohexanone (XXXVI). The nmr spectrum of Compound XXXIV was identical with that reported by Conia and Briet (35). The characterization of isomers of XXXV is given below. Compound XXXVI was not characterized fully, but a sample prepared

by VPC (10-ft x 0.25-in column, 15 per cent 4-MNP on 60/80 firebrick) gave the following nmr spectrum: nmr* ($CCl_4$) $\delta$ 2.58-1.25 (broad absorption), 1.13 (s), 1.08 (d, J=6 Hz), 0.97 (d, J=6 Hz), 1.00 (s) and 0.91 ppm (s, $C(CH_3)_3$).

Methylation of the Kinetic Mixture of Lithium Enolates from cis-2-Methyl-4-t-butylcyclohexanone (XI)

A solution of trityl lithium was prepared from 2.73 g (0.0112 mol) of triphenylmethane, 100 ml of DME, and 0.009 mol of phenyl lithium (1.8 M in 70:30 benzene:ether). Then 1.45 g (0.0080 mol) of XI (93 per cent cis) was titrated into the solution. After stirring for 30 min the solution was reacted with 8.52 g (0.060 mol) of methyl iodide. VPC analysis (10-ft x 0.25-in column, 15 per cent 4-MNP on acid washed firebrick) showed the following: XXXIV (14.1 per cent), XXXV (79.7 per cent), XXXVI (6.2 per cent). No starting material (XI) could be detected. Distillation yielded 1.25 g, bp 62-68° (0.4 mm), of the same composition. The isomeric composition of the dimethyl compounds could be determined by a combination of VPC and nmr spectroscopy. All isomers could be separated using the 4-MNP column and were eluted in the following order: XXXVI, XXXV (both methyl groups cis to the t-butyl group (XXXVa)), XXXIV, XXXV (methyl groups trans to each other (XXXVb)), cis-XI, trans-XI, and finally 4-t-butylcyclohexanone. It proved to be difficult to detect small amounts of XXXVa in XXXIV and *vice versa*. Here an estimate could be made by nmr spectroscopy based on the methyl

*There was extensive overlap of the peaks in the methyl region so that areas could not be unequivocably assigned.

group absorbing at 1.12 ppm in XXXIV. From this run a sample of XXXVb was collected by VPC and showed the following properties: ir ($CCl_4$) 1710 $cm^{-1}$ (C=O); nmr ($CCl_4$) $\underline{\delta}$ 2.75-1.25 (broad absorption, 7), 1.13 (d, 3, J=7.5 Hz, axial $CHC\underline{H}_3$), 0.97 (d, 3, J=6 Hz, equatorial $CHC\underline{H}_3$), and 0.90 ppm (s, 9, $C(C\underline{H}_3)_3$); mass spectrum 70 eV $\underline{m/e}$ (rel intensity) 182 (57), 126 (77), 57 (91), and 41 (100); exact mass 182.165, calcd. for $C_{12}H_{22}O$--182.166. Compound XXXVa is characterized below. Using the combined techniques the ratio of XXXVb to XXXVa in the alkylation is 1.8 to 1 corresponding to 51.4 per cent and 28.3 per cent in the product mixture.

Methylation of the Kinetic Mixture of Lithium Enolates of trans-2-Methyl-4-t-butylcyclohexanone

A solution of trityl lithium was prepared from 2.73 g (0.0112 mol) of triphenylmethane, 100 ml of DME and 0.009 mol of phenyl lithium (1.8 M in 70:30 benzene:ether). Then 1.45 g (0.0080 mol) of XI (75 per cent trans) was introduced slowly into the red solution. When the resulting solution had stirred for 30 min, 8.42 g (0.060 mol) of methyl iodide was added rapidly. VPC analysis (10-ft x 0.25-in column, 15 per cent 4-MNP on acid washed firebrick) of the crude product yielded the following: XXXVa (11.2 per cent), XXXVb (58.7 per cent), XXXIV (4.5 per cent), XXXVI (10 per cent), and 15.6 per cent of another product with retention time different from XI or any of the other compounds. The compound appears on the chromatogram as a shoulder on the trailing edge of the peak for XXXVb. Because refluxing the distilled mixture overnight with 10 per cent HCl converts the dimethyl fraction into an equilibrium

mixture of isomers consisting of 85 per cent XXXVa and 15 per cent XXXVb with no spurious products, the unknown peak was presumably XXXV with both methyl groups cis to each other and trans to the t-butyl moiety (XXXVc). Distillation yielded 1.28 g of a mixture, bp 60-70° (0.4 mm), of the same composition. A sample of XXXVa was prepared by VPC and exhibited the following properties: ir ($CCl_4$) 1715 $cm^{-1}$ (C=0); nmr ($CCl_4$) $\delta$ 2.75-1.25 (broad absorption, 7), 0.96 (d, 6, J=6 Hz, $CHCH_3$) and 0.91 ppm (s, 9, $C(CH_3)_3$); nmr ($C_6H_6$) $\delta$ 1.00 (d, J=6 Hz, $CHCH_3$) and 0.78 ppm (s, $C(CH_3)_3$); mass spectrum 70 eV m/e (rel intensity) 182 (33), 126 (56), 57 (100), and 41 (27).

To ascertain the ratio of isomers from the lithium enolate of trans-XI, it was necessary to correct for the amount of cis-XI present. Since all XXXVa must have come from cis-XI, a corresponding amount of the XXXVb observed in this alkylation must be attributed to the enolate from cis-XI. Thus, the ratio of XXXVb to XXXVc became about 2.5 to 1 which was the preference for twist boat alkylation. Finally the minute amount of XXXIV formed indicated that the kinetic lithium enolate of trans-XI was essentially 100 per cent the less substituted enolate.

Trideuteromethylation of the Equilibrium Mixture of Lithium Enolates of 2-Methyl-4-t-butylcyclohexanone (XI)

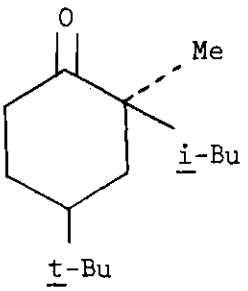
A solution of trityl lithium was prepared from 2.73 g (0.0112 mol) of triphenylmethane, 100 ml of DME, and 0.0090 mol of phenyl lithium (1.8 M in 70:30 benzene:ether). After titrating in 1.61 g (0.0089 mol) of XI to discharge the red color, 0.20 g (0.0011 mol) of XI was added in excess. After equilibration by heating for three hours

at reflux, the enolate solution was cooled and reacted with 8.42 g (0.058 mol) of methyl iodide. After the general work-up, distillation yielded 1.35 g of material, bp 50-60° (0.2 mm). The 2,2-dialkyl product was collected by VPC (10-ft x 0.25-in column, 15 per cent 4-MNP on acid washed firebrick) and analyzed by nmr spectroscopy. The down-field methyl singlet at $\underline{\delta}$ 1.12 ppm (35) was only 29.4 per cent of the singlet at $\underline{\delta}$ 1.00 ppm (35). By analogy with trans-XI the down-field methyl singlet is assigned to the axial methyl group. Since the down-field singlet was diminished, the major fraction (2.4 to 1) of the trideuteromethyl group has been introduced in the axial position. The mass spectrum of the collected sample showed the following: 70 eV m/e (rel intensity) 185 (69), 129 (88), and 57 (100).

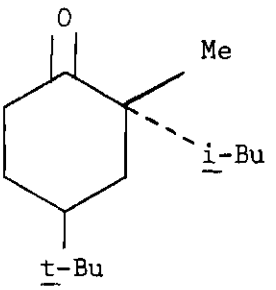
Isobutylation of the Equilibrium Mixtures of Metal Enolates of 2-Methyl-4-t-butylcyclohexanone

A solution of trityl potassium was prepared from 0.35 g (0.0090 mol) of potassium metal, 15 ml of DME, 2.44 g (0.0100 mol) of triphenylmethane, and 1 ml of 1,3-butadiene. An additional 60 ml of DME was added, and 1.14 g (0.0068 mol) of XI was titrated into the solution to discharge the red color. After adding 0.25 g (0.0015 mol) of XI in excess and stirring for one hour, 3.31 g (0.018 mol) of doubly distilled isobutyl iodide was added. The mixture was stirred overnight at room temperature under nitrogen. After conventional work-up, the mixture of ketones was distilled to yield 1.2 g of material, bp 70-130° (1 mm). Analysis by VPC (10-ft x 0.25-in column, 20 per cent-XE-60 on acid washed firebrick) showed that the mixture contained 40 per cent XI and

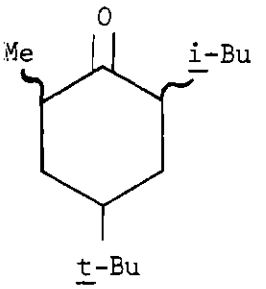
60 per cent of a mixture of dialkyl ketones. The composition of the dialkyl fraction was determined to be 54.5 per cent XXXVIIa*, 38.2 per cent XXXVIIb* and presumably 7.3 per cent 2-isobutyl-6-methyl-4-t-butylcyclohexanone (XXXVIII).




XXXVIIa




XXXVIIb




XXXVIII

Compound XXXVIIa was identified by its melting point (mp 41-42° (lit. (35) 42°) and its nmr spectrum reported by Conia and Briet (35). The mass spectrum of XXXVIIa revealed the following: 70 m/e (rel intensity) 224 (0.1), 182 (0.5), 168 (100) and 57 (71). Compound XXXVIIb was identified by comparing its VPC behavior and nmr spectrum with that reported previously (35). The mass spectrum of XXXVIIb exhibited the following: 70 eV m/e (rel intensity) 224 (0.1), 182 (17), 168 (100), and 57 (71). Compound XXXVIII was not characterized.

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*The stereochemical assignment given here is that reported by Conia and Briet (35, 62). The assignment is not on an unequivocal basis, and evidence gathered in this research suggests the opposite stereochemistry for XXXVIIa and XXXVIIb. See Chapter IV.

A solution of trityl lithium was prepared from 1.62 g (0.0066 mol) of triphenylmethane, 60 ml of DME and 0.0050 mol of phenyl lithium (1.72 M in 70:30 benzene:ether). The red color was discharged by titrating 0.79 g (0.0047 mol) of XI in 12 ml of DME into the solution. After 0.14 g (0.0008 mol) of XI was introduced in excess, the solution of enolates was stirred at reflux for three hours. Alkylation with 2.60 g (0.014 mol) of doubly distilled isobutyl iodide was accomplished by stirring 16 hr at room temperature. Analysis of the alkylated mixture by VPC (10-ft x 0.25-in column, 20 per cent XE-60 on acid washed firebrick) determined the composition of the mixture--XXXVIIa (55.3 per cent), XXXVIIb (33.1 per cent) and XXXVIII (11.6 per cent).

# CHAPTER IV

## DISCUSSION OF RESULTS

In order to gain information related to the problem of specific alkylation in unsymmetrical ketones, three avenues of investigation, generation of specific metal enolates, the rates of alkylation of suitable systems, and the stereochemistry of alkylation of model ketones, were examined in detail. Accomplishing the specific alkylation of unsymmetrical ketones by a simple base-catalyzed process requires the generation of a specific metal enolate anion and an alkylating agent that reacts with the enolate anion faster than the latter equilibrates *via* proton transfer reactions. Thus, a suitable base must possess sufficient reactivity to convert the unsymmetrical ketone completely into its corresponding enolate anion. The most stringent condition imposed on the base is that it must exhibit significant selectivity in removing a particular α-proton. Finally, the conjugate acid of the base used to generate the specific metal enolate anion must not be strong enough to equilibrate the enolate anion between its two possible isomeric entities. Hence, alkoxides, which yield reactive alcohols, are not suitable ordinarily; on the other hand, trityl bases, yielding triphenylmethane in the course of enolate formation, do provide an amenable system with regard to the strength of the conjugate acid.

Equilibration *via* proton transfer may occur with any excess starting ketone destroying any selectivity delivered by the base or with

the initially alkylated product providing a new enolate anion that can compete for the alkylating agent. As shown in Figure 1, a very complicated mixture of products results when proton transfer is faster than or competitive with alkylation. Two isomeric monoalkylated products result immediately. Each of these can be converted into enolate anions, undergo equilibration with other anions in the system and suffer alkylation yielding two other products as well as converting a portion of the original enolate into starting ketone. Thus, at least four products, 2-alkyl-, 2,2-dialkyl-, 2,6-dialkyl-, and 2,2,6-trialkylcyclohexanone, result, and it is certainly possible for K (Figure 1) to enter into the equilibrating system to produce even another enolate anion.

## Generating Specific Enolate Anions

### Reaction of Ketones with Trityl Bases

Trityl bases exhibit the capacity for converting ketones completely to the corresponding enolate anions and a weak conjugate acid. Trityl lithium, then, becomes a candidate for use in a directed alkylation, if it possesses a sufficient degree of selectivity, because lithium enolates do react with relatively reactive alkylating agents faster than they equilibrate. An investigation was performed to determine the selectivity of proton removal from model unsymmetrical ketones by trityl lithium and factors affecting the selectivity. Trityl potassium was employed for comparison. Two ketones, 2-methylcyclohexanone (IX) and 2-methyl-4-t-butylcyclohexanone (XI), were converted to kinetic and equilibrium mixtures of enolate anions in DME and quenched with acetic anhydride (49) or methyl iodide.

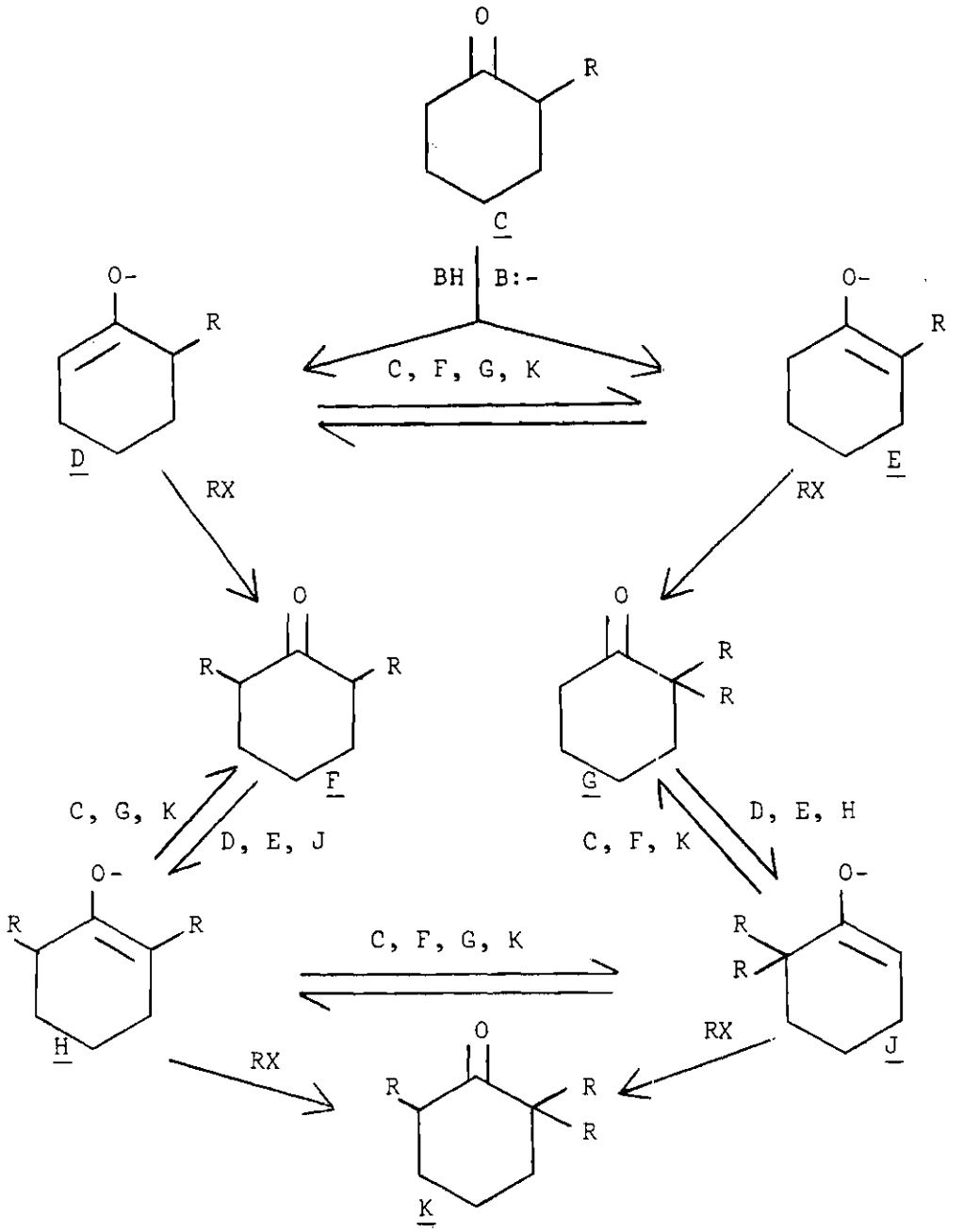



Figure 1. Alkylation Scheme for an Unsymmetrical Ketone

Enolate anion compositions determined by nmr spectroscopy on the enol acetate mixtures are reported in Table 2. Under kinetic conditions, which imply the presence of excess base after enolate anion formation is complete, trityl lithium shows a six-fold preference for the C-6 proton in IX and cis-XI. The slower rate of removal of the proton on the more substituted carbon atom is in agreement with the observation of Maron and La Mer (63) that the introduction of an alkyl group on the α-carbon atom of a nitroalkane lowers the velocity constant in the reaction with hydroxyl ion by a factor of ten. Subrahmanyam and co-workers (64) observed that the rate of proton removal from C-6 in androst-4-ene-3,17-dione by potassium t-butoxide in t-butyl alcohol was faster than that from the 6-methyl derivative. The difference may be attributed to both electron release by the methyl group and steric crowding (65) of the transition state for proton removal at C-2. The effect of temperature again reflects a difference in the rate of proton removal; the slower process requiring the larger activation energy becomes less important as the temperature decreases. THF and DME show no significant difference in influence at -80° on the reaction of IX with trityl lithium.

Under equilibrium conditions, which imply an excess of ketone available after complete enolate anion formation and enough time to allow equilibration, the more substituted enolate anion is favored. The increased stability for the more substituted enolate anion reflects the stabilizing influence of an alkyl group on an olefin.

Table 2. Compositions for Thermodynamic and Kinetic Mixtures of Isomeric Metal Enolates of Unsymmetrical Ketones

| Ketone | Metal | Enolate Type | Solvent | Temp | Enolate[a] Composition %LS[b] | %MS[b] |
|---|---|---|---|---|---|---|
| IX | Li | Kinetic | DME | 25° | 86 | 14 |
| IX | Li | Kinetic | DME | -80° | 90 | 10 |
| IX | Li | Kinetic | DME | 84° | 78 | 22 |
| IX | Li | Kinetic | THF | -80° | 92 | 8 |
| IX | Li | Eqm[c] | DME | -[d] | 10 | 90 |
| IX | K | Kinetic | DME | 25° | 68 | 32 |
| IX | K | Eqm | DME | 25° | 30[e] | 70[e] |
| cis-XI[f] | Li | Kinetic | DME | 25° | 86 | 14 |
| cis-XI | Li | Eqm | DME | -[d] | 11 | 89 |
| cis-XI[f] | K | Kinetic | DME | 25° | 68 | 32 |
| cis-XI | K | Eqm | DME | 25° | 31 | 69 |
| trans-XI[f] | K | Kinetic | DME | 25° | 100 | 0 |
| trans-XI[g] | Li | Kinetic | DME | 25° | 100 | 0 |

[a]Average of two trials.

[b]LS = less substituted enolate anion; MS = more substituted anion.

[c]Equilibrium or thermodynamic.

[d]The equilibration was carried out at 84° and the mixture cooled before quenching; therefore, a specific temperature cannot be assigned to the equilibrium values.

[e]House and Kramar (15) reported a 35/65 ratio for this same mixture.

[f]Calculated values--See Appendix A for the data determined on mixtures containing 93 per cent cis-XI and 75 per cent trans-XI, respectively.

[g]Estimated from methylation results on a kinetic mixture of lithium enolates from 75 per cent trans-XI.

Kinetic mixtures of enolate anions from IX and cis-XI produced by trityl potassium reflect the greater reactivity with a consequent decrease in selectivity for this base. The position of equilibrium also lies further toward the less substituted enolate anion for potassium as compared to lithium. The explanation for this situation lies in the fact that the oxygen-lithium bond is more covalent than the oxygen-potassium bond in metal enolates resulting in a greater fraction of the negative charge residing on carbon in the potassium enolates. Since a secondary carbanion is more stable than a tertiary carbanion, the electron release of the methyl group mitigates against the stability of the more substituted isomer. The size of the solvated ion pair is also a factor, even though the steric requirement is unsymmetrical with the greatest bulk directed toward C-6 (64), and this will be considered in more detail below.

Finally, even a base as reactive as trityl potassium shows virtually complete stereoselectivity in forming an enolate anion from trans-XI. In Figure 2 the conformational geometry of trans-XI is shown.

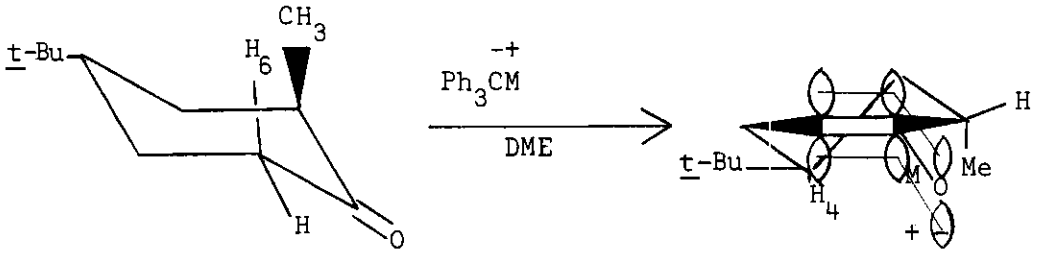
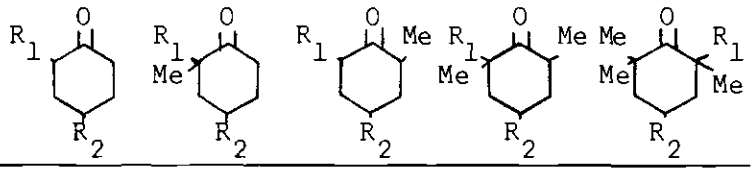



Figure 2. The Reaction of trans-2-Methyl-4-t-butylcyclohexanone (XI) with Trityl Bases

Clearly, the only axial proton available is located on C-6. Since stereoselectivity is observed, the rate of removal of this proton is large compared to the rate for the proton at C-2. The axial proton is considered to be more easily removed because the developing p-orbital can enjoy overlap with the π-electrons of the carbonyl group right away (27, 66). At C-2 the proton must be withdrawn without the benefit of overlap, or the ring must assume a twist conformation in order to provide a path for stereoelectronic control. Both processes would be expected to require more energy than removal of the axial C-6 proton in the chair conformation, hence, to be slower. Subrahmanyam, *et al.*, (64) observed that the rate of proton removal of the 6β-proton (axial) in androst-4-ene-3,17-dione is 53 times faster than the rate for the 6α-proton (equatorial). The generation of a specific enolate anion from trans-XI indicates the utility of trityl bases and emphasizes in a rigid system the importance of continuous σ-π overlap of the proton departing under the influence of a strong base.

To be useful in alkylation enolates selectively formed should yield alkylated products in good yield with no significant equilibration among the enolates prior to or during the alkylation. Product compositions from reaction of various types of enolate mixtures with methyl iodide are recorded in Table 3. For mixtures of lithium enolates the respective amounts of 2,2-dialkyl material and 2,6-dialkyl material generally reflect the percentages determined by acetic anhydride quenching. In addition, the yield of monoalkylated products is good for lithium enolates and polyalkylation is not a serious problem. The

Table 3. Product Compositions from Kinetic and Equilibrium Mixtures of Metal Enolates from Unsymmetrical Ketones Reacting with Methyl Iodide in DME at 25°

| $R_1$ | $R_2$ | Metal | Enolate Type | Enolate Formation Temp | PRODUCT COMPOSITION (PERCENTAGE)  | | | | |
|---|---|---|---|---|---|---|---|---|---|
| Me | H | Li | Eqm | 25° | 15[a] | 70 | 8 | 7 | 0 |
| Me | H | Li | Kin | -80° | 5 | 9 | 71 | 15 | 0 |
| Me | H | Li | Kin[b] | -80° | 8 | 8 | 76 | 8 | 0 |
| Me | H | K | Kin | 25° | 12 | 27 | 30 | 27 | 4 |
| Me | H | K | Kin[c] | 25° | 7 | 50 | 11 | 27 | 5 |
| Me | H | K | Eqm[d] | 25° | 25 | 41 | 10 | 24 | 1 |
| Me | t-Bu | Li | Eqm | 25° | 28[e] | 53 | 5 | 13 | 0 |
| Me | t-Bu[f] | Li | Kin | 25° | 0 | 14 | 79 | 7 | 0 |
| Me | t-Bu[g] | Li | Kin | 25° | 0 | 4 | 86 | 10 | 0 |

[a]10 Per cent excess ketone used for equilibration. [b]THF solvent. [c]The methyl iodide was added dropwise. [d]See Reference 12. [e]25 Per cent excess ketone used for equilibration. [f]A mixture containing 93 per cent cis-XI was employed. [g]A mixture containing 75 per cent trans-XI was used.

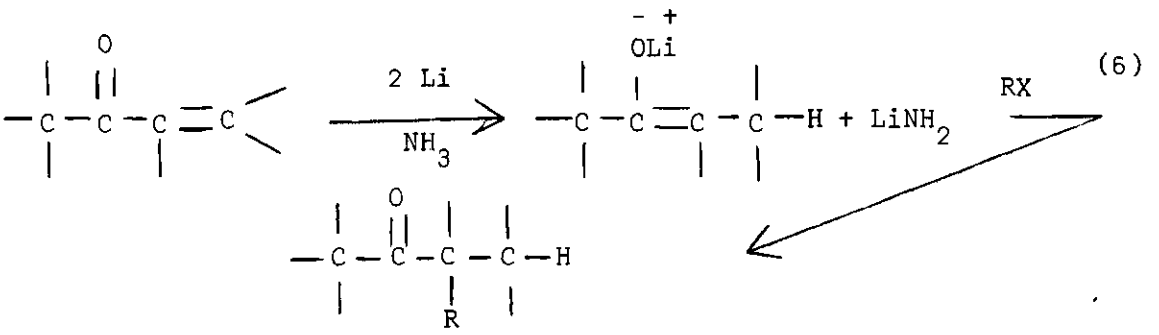
situation is different for potassium enolates in that polyalkylation is a very serious problem and enolate equilibration is competing with alkylation. As a matter of fact, dropwise addition of methyl iodide to a kinetic mixture of potassium enolates of IX results in a product distribution tantamount to that obtained from an equilibrium mixture of potassium enolates of IX. Finally, from the small amount of 2,2-dialkyl material produced in the methylation of the kinetic mixture of lithium enolates of XI (75 per cent trans), it is apparent that the reaction of trans-XI with trityl lithium in DME generates the less substituted enolate specifically.

The significant selectivity of trityl lithium in proton removal particularly with respect to trans-XI and 2-isopropylcyclohexanone, which also yields the less substituted enolate specifically with trityl lithium (67), suggests that trityl bases could be tailored to give the less substituted enolate in an unsymmetrical system of interest. By placing electron-donating or electron-withdrawing groups on the aromatic rings of the trityl anion, its reactivity and steric requirement could be altered significantly. Coupling this possibility with a slow equilibration rate, lithium enolates offer synthetic applicability without major separation problems for relatively volatile ketones.

Lithium-Liquid Ammonia Reduction and Reduction-Methylation of α,β-Unsaturated Cyclohexanone Derivatives

In general terms, the reduction-alkylation procedure involves the generation of a specific lithium enolate of an unsymmetrical ketone by reduction of the corresponding α,β-unsaturated or α-haloketone with

two equivalents of lithium in liquid ammonia and the reaction of this enolate with an alkylating agent either in liquid ammonia or other solvent systems (eq 6). If ammonium chloride is used in lieu of RX the saturated ketone is produced. Of course, the success of the methods depends upon the now well-established fact that alkylation of specific lithium enolates (as opposed to other alkali metal enolates) of unsymmetrical ketones with relatively reactive alkylating agents occurs faster than does equilibration among the structurally isomeric enolates via proton-transfer reactions (11, 68).




The interest in directing alkylation to specific α-positions prompted the study of the reduction-methylation of several cyclohexenone derivatives including 2-methyl-2-cyclohexen-1-one (XII), 6-methyl-2-cyclohexen-1-one (XIII), 4,4,6-trimethyl-2-cyclohexen-1-one (XVI), and 3-methyl-2-cyclohexen-1-one (XIV), as well as 2-chloro-2-methylcyclohexanone (XVII). In order to determine the optimum conditions for carrying out the first step in the reduction-alkylation procedure, that is, the generation of the lithium enolate, the simple lithium-liquid ammonia reduction of some of these enones as well as 7β-isopropyl-10α-methyl-

$\Delta^{1(9)}$-octalone-2 (XV) was investigated. The results of these studies are recorded in Table 4.

Table 4. Lithium-Liquid Ammonia Reduction of Cyclohexenone Derivatives

| Enone | Proton Donor (1 equiv) Added | Yield of Recovered Ketones (Percentage) | |
|---|---|---|---|
| | | Starting Enone | Reduction Product |
| XII | t-BuOH | 0 | 50[a] |
| XII | None | 15[b] | 47[b] |
| XII | $H_2O$ | 0 | 48[b] |
| XVI | t-BuOH | 0 | 80[b] |
| XIV | t-BuOH | 0 | 62[a] |
| XIV | None | 0 | 66[b] |
| XV | t-BuOH | 0 | 70[a] |

[a]Yield determined on the basis of the quantity of distilled product recovered.

[b]Yield determined by VPC analysis using m-xylene as an internal standard.

Compounds XII and XVI are cyclohexenone derivatives which are unsubstituted in the β-position. When the reduction of these compounds was carried out in the usual manner by dropwise addition of the enone in anhydrous ether to a solution of lithium in anhydrous liquid ammonia followed by addition of excess ammonium chloride and work-up, VPC analysis showed that the volatile products consisted of the α,β-dihydro derivative contaminated with a considerable quantity of unchanged

starting material (Figures 3 and 4). (Similar results have been obtained in cases in which the reverse procedure of addition of lithium metal to a solution of the enone in liquid ammonia was employed.*) However, in each case in which the reduction was conducted in exactly the same manner as above, except that an equivalent amount of a proton donor (usually anhydrous t-butyl alcohol) was added along with the enone to a solution of lithium in liquid ammonia, the α,β-dihydro derivative was the only volatile material obtained after addition of ammonium chloride. Thus, in these cases the addition of t-butyl alcohol along with the enone led to improved yields of reduced ketones and made it possible to obtain a pure product by simple distillation of the reaction mixture. As indicated in Table 4, the enone XIV having a methyl substituent at the β-position was reduced smoothly to 3-methylcyclohexanone (XXVII) regardless of the presence of the equivalent of alcohol in the reduction scheme.

The addition of alcohols has been employed in a number of instances in order to improve yields in metal-ammonia reductions of α,β-unsaturated ketones (69, 70). In cases where excess alcohol is used, the enone is reduced to the corresponding saturated alcohol and an oxidation step is required in order to obtain the corresponding saturated ketone. However, when one equivalent of alcohol was employed

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*In an experiment performed by Dr. H. A. Smith (31c) 2,4,4-trimethyl-2-cyclohexen-1-one in ether was added to liquid ammonia followed by two equivalents of lithium. The product analysis showed that 47 per cent of the recovered material was starting enone and 53 per cent was the corresponding α,β-dihydro derivative.

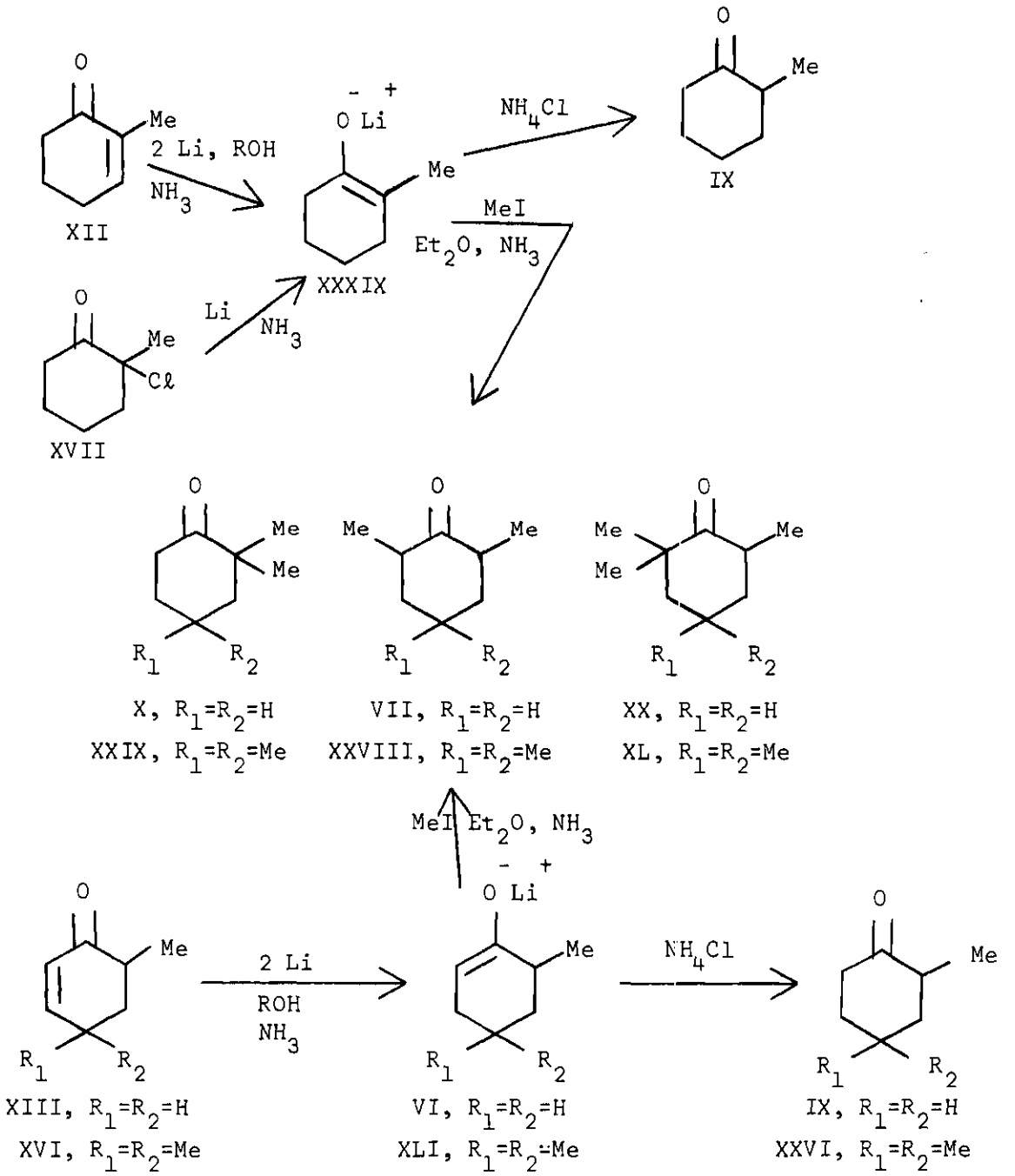


Figure 3. Reduction-Methylation Scheme for α,β-Unsaturated Cyclohexanone Derivatives and α-Haloketones

under the reaction conditions described above, no more than trace quantities of alcohols were obtained from any of the enones studied.

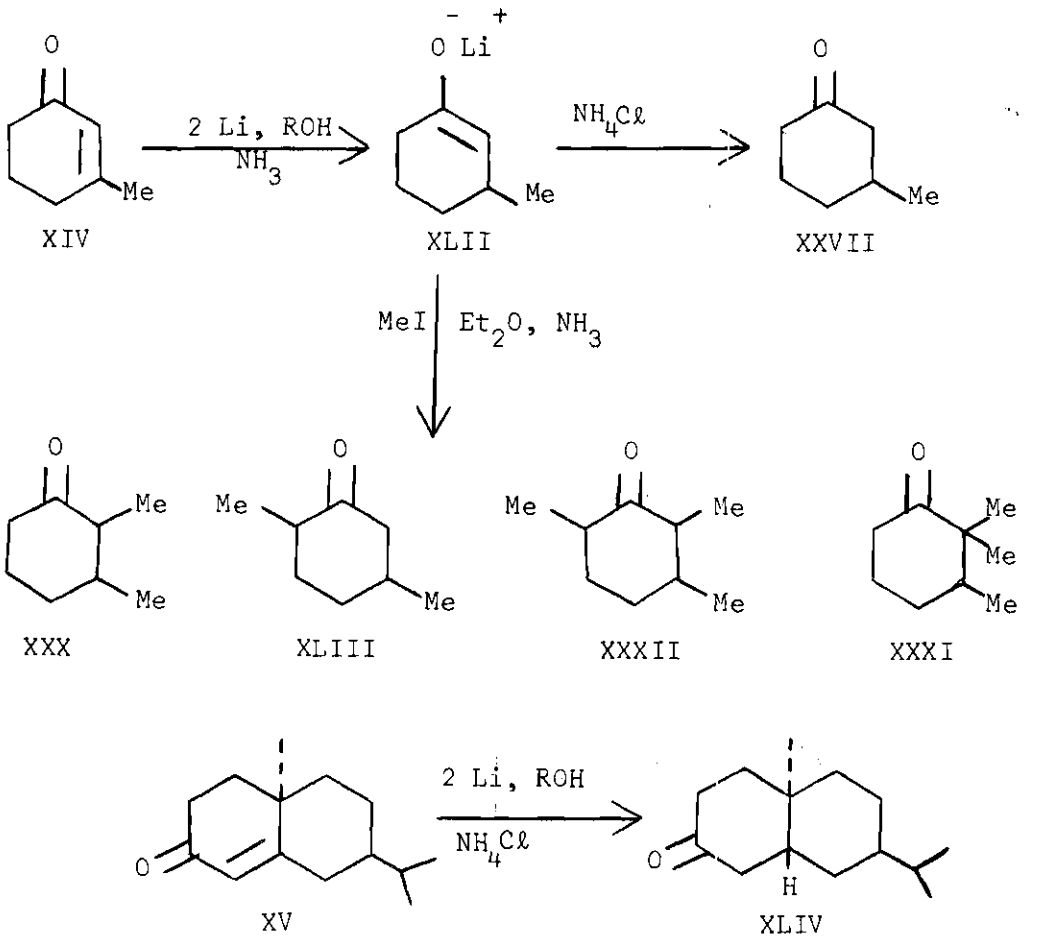


Figure 4. Reduction-Methylation Scheme for 3-Methyl-2-cyclohexen-1-one (XIV) and the Reduction of 7β-Isopropyl-10α-methyl-$\Delta^{1(9)}$-octalone-2 (XV)

Regarding the recovery of unreacted starting material, a few examples are available in which the recovery of enone is a complicating factor and in which it is not. Recovered starting material has been

observed in the metal-ammonia reduction of 3-ethylenedioxy-16-dehydroprogesterone (11) in the absence of an added proton donor. Stork and co-workers did not observe recovered starting material in the reduction of a β-substituted $\Delta^{1(9)}$-octalone-2 (68) with no added proton source. Conia and Rouessac (71) reported the reduction of a β-substituted cyclohexenone derivative without benefit of an added proton source in which the recovery of unchanged starting material* was not an apparent complication. The complete reduction of XIV in the absence of a proton donor merely emphasizes the difference in behavior of β-substituted and β-unsubstituted cyclohexenone derivatives.

The role of the proton donor in bringing about more complete reduction of the β-unsubstituted enones has not been definitely established. One possibility is that in these cases it serves to prevent competing side reactions of the enone with lithium amide, formed as the reaction proceeds, which lead to its deactivation toward reduction. Conjugate enolate formation or 1,2- (72) or 1,4-addition are possible reactions of the enone with lithium amide which would convert it into a species which resists reduction but from which it could be regenerated on work-up of the reaction mixture. The proton donor might prevent such

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*The compound investigated by Conia and Rouessac (71) was 2-methyl-3-(4'-pentenyl)-2-cyclohexen-1-one.

reactions either by increasing the rate of reduction* or simply reacting with the lithium amide as it is formed, or both. Conjugate enolate formation has been proposed in order to explain results in reduction-alkylations of 3-ethylenedioxy-16-dehydroprogesterone (11). However, no unsaturated alkylation products were observed with reduction-methylation of XII in the absence of a proton donor (see Chapter III). This suggests that conjugate enolate formation is not an important side reaction in the reduction of this compound and that it is not likely to be very important for the other cyclohexenones studied. Thus amide addition reactions are likely to be responsible for the recovery of unreacted enone in the reductions of XII (and 2,4,4-trimethyl-2-cyclohexen-1-one mentioned above) when no proton donor is added.

The results of reduction-methylation of XII, XIII, XIV, XVI, and XVII are shown in Table 5 and in Figures 3 and 4. The enones were converted to the corresponding lithium enolates under the same conditions as described in the reduction reactions using t-butyl alcohol. Then the reaction mixture was diluted with an approximately equal volume of ether, and an approximately five-fold excess of methyl iodide was added

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*Because of the presence of the methyl substituent at the β-position the radical anion or dianion (it is not certain which of these species is actually protonated (69)) derived from addition of one or two electrons to XIV should be more basic than similar species derived from XII or XVI. Thus, if β-protonation is the rate-determining step in metal-ammonia enone reductions, XIV would be expected to undergo reduction faster than the β-unsubstituted enones. This is a likely reason that the proton donor is not required to prevent recovery of unreacted starting material in the reduction of XIV.

Table 5. Reduction-Methylation of Cyclohexenone Derivatives and 2-Chloro-2-methylcyclohexanone

| Enone | Proton Donor (1 equiv) Added | Composition of Recovered Mixtures of Ketones, Percentage | | | | Yield % |
|---|---|---|---|---|---|---|
| | | IX | X | VII | XX | |
| XII | t-BuOH | 2 | 80 | 0 | 18[a] | 49[b] |
| XII | $H_2O$ | 2 | 96 | 0 | 2 | 63[c] |
| XII | None | 2 | 57[d] | 0 | 2 | -[e] |
| XIII | t-BuOH | 12 | 0 | 86 | 2 | 43[b] |
| | | XXVI | XXIX | XXVIII | XL | |
| XVI | t-BuOH | 5 | 0 | 95 | 0 | 60[c] |
| | | XXX | XLIII | XXXII | XXXI | |
| XIV | t-BuOH | 87 | 0 | 13[f] | | 54[b] |
| | | IX | X | VII | XX | |
| XVII[g] | None | 2 | 98 | 0 | 0 | 85[c] |
| XVII[h] | None | 50 | 50 | 0 | 0 | -[e] |

[a]Mixtures having identical compositions were obtained in duplicate reduction runs on XII.

[b]The yield is based on the quantity of material distilled considering it to be only the monoalkylation product.

[c]The yield of monoalkylation product calculated by VPC analysis using m-xylene as an internal standard.

[d]The remaining 39 per cent proved to be XII.

[e]The yield was not determined.

[f]The structure of this component of the alkylation mixture was not definitely established, but it was assumed to be XXXI or XXXII or a mixture of the two.

[g]Enolate concentration = 0.04 M.

[h]Enolate concentration = 0.41 M.

dropwise over about 30 min. Examination of the data in Tables 4 and 5 shows that the yields in the corresponding reduction reactions are approximately equal to the yields in the reduction-alkylations. This observation implies that the alkylation step in the sequence takes place in high yields. The loss of yield in the reduction is probably due to side reactions such as aldol condensation or bimolecular reduction (73) which can compete with enolate formation even in the presence of an added proton donor. Only trace amounts (usually less than 10 per cent of the recovered mixture of ketones) of simple reduction products were obtained in the reduction-methylation runs. These products could arise by reaction of the lithium enolates with the added proton donor, traces of protonic impurities in the solvent, or with methylammonium iodide produced by the reaction of the liquid ammonia with the methyl iodide. That the last case is a likely possibility has been demonstrated by Smith and co-workers (74) who added the enolate solution to methyl iodide that had been dissolved in liquid ammonia long enough to allow some methylammonium iodide to form and recovered in large proportion merely reduced starting material.

As indicated in Table 5, page 73, in each case the reduction-methylation procedure yielded only the monoalkylation product derived from alkylation of the specific lithium enolate produced in the reduction reaction. As mentioned earlier the rate of equilibration of lithium enolates often allows trapping of these species, and apparently no interconversion among the more (XXXIX) and less (VI) substituted enolates derived from IX or the $\underline{\Delta}^{1(2)}$-(XLII) or $\underline{\Delta}^{1(6)}$-enolates derived from XXVII

occurs under the conditions of the alkylation step. The procedure thus provides a convenient means of synthesizing selectively alkylated cyclohexanone derivatives in cases where the necessary starting enones are available.

The direct conversion of XIV into 2,3-dimethylcyclohexanone (XXX) offers an interesting example of the utility of the reduction-alkylation procedure. 2-Alkyl-5-methylcyclohexanones are the only monoalkylation products obtained either by direct base-catalyzed alkylation of XXVII (75) or even by indirect methods that work well in other systems (6). The allylic strain (76) in the $\Delta^{1(2)}$-enolate (XLII) is apparently not of sufficient magnitude to prevent the formation of XLII nor does it produce a sufficient driving force to equilibrate the lithium enolates of XXVII in the ammonia-ether system.

It may be observed from Table 5 that increasing the concentration of XVII added to liquid ammonia from 0.04 M to 0.41 M completely changes the product distribution. The precise explanation for this phenomenon is not known. Another observation from Table 5 is that polyalkylation as a result of base-catalyzed (either by lithium amide or lithium t-butoxide) conversion of monoalkylated materials into their enolate anions and subsequent alkylation, occurred to a significant extent in the reduction-methylation of XII and probably also in the case of XIV. However, the formation of the trimethyl ketone XX could almost be eliminated if an equivalent amount of water was substituted for t-butyl alcohol. It is particularly interesting that a significant quantity of XX was produced in runs involving XII but not in those

involving XIII conducted under identical conditions. This suggests that the over-all process of lithium enolate formation and methylation is faster for 2,2-dimethylcyclohexanone (X) than for 2,6-dimethylcyclohexanone (VII) under the reaction conditions. The results of other studies demonstrate that with potassium or sodium enolates of mixtures of VII and X the symmetrical ketone VII undergoes polyalkylation faster than X in ether and alcohol solvents (15, 77).

In order to compare the utility of sodium in reductive alkylation of simple cyclohexenone derivatives, 6-methyl-2-cyclohexen-1-one (XIII) was reduced by sodium in liquid ammonia and methylated in ether-ammonia. A very complicated product mixture was isolated in which the two major products were 2,2,6,6-tetramethylcyclohexanone (XXV) and an unidentified alcohol. There were at least two other minor products. Weiss and coworkers (11) used sodium successfully, however, in alkylating 16-dehydroprogesterone derivatives. With XIII enolate equilibration and further reduction are serious complications.

## Kinetics of Alkylation

Fundamental to the problem of specific alkylation of unsymmetrical ketones is a knowledge of the factors affecting the rate of alkylation at each type of α-position. For example, if reaction occurred at one position many times faster than at the other position, it would be possible to prepare a specific product from a mixture of isomers obviating the generation of specific enolates. For adequate interpretation of kinetic data on alkylation it is beneficial to consider first expected steric and electronic factors involved in alkylating the more (XXXIX) and the

less (VI) substituted enolate anions derived from an unsymmetrical system such as 2-methylcyclohexanone (IX).

General Steric and Electronic Factors

Considering VI and XXXIX, some of the factors that could be involved in determining the rate of alkylation of isomeric enolate anions of IX may be discussed. The methyl group on the double bond in the enolate anion XXXIX would be expected to enhance the nucleophilicity of the carbon atom undergoing alkylation; however, it could also exert a rate retarding steric effect (65). In VI, as is shown in Figure 5, the methyl group may assume a quasiaxial or a quasiequatorial conformation. The exact percentages of each conformer depend on the magnitude of the interaction between the quasiequatorial methyl group and the cation solvent shell (61). In a stereoelectronic axial alkylation, illustrated in Figure 6, the conformer with the methyl group quasiaxial would be expected to be alkylated slowly because of the 1,3-interaction between the methyl group and the alkylating agent. To the extent that this conformer is present the reactivity of VI would be expected to be reduced.

Alkylation of Metal Enolates of Cyclohexanone Derivatives

The rates of alkylation of the lithium and potassium enolates of 2,2- (X) and 2,6-dimethylcyclohexanone (VII), the equilibrium mixture of potassium enolates of 2-methylcyclohexanone (IX) and the two lithium enolates from cis-2-methyl-4-t-butylcyclohexanone in DME are summarized in Table 6. (See Appendix B for complete data.)

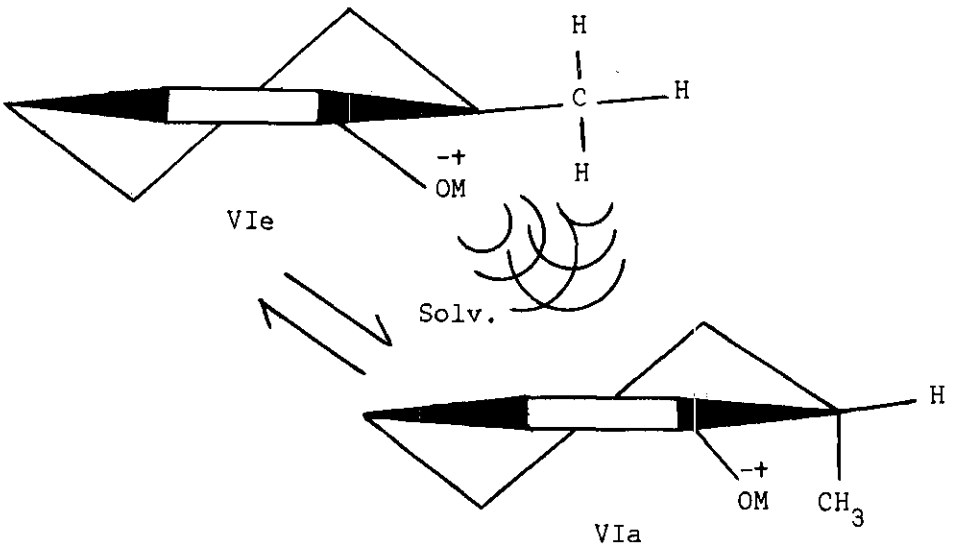



Figure 5. Conformational Equilibrium in the Less Substituted Metal Enolate of 2-Methylcyclohexanone

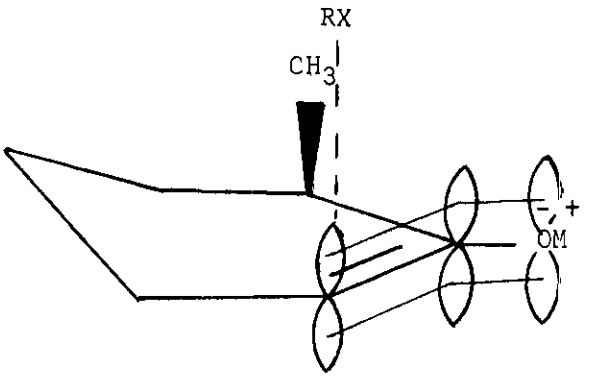



Figure 6. Stereoelectronically Controlled Axial Alkylation of the Less Substituted Enolate of IX

Table 6. Rates of Alkylation of Metal Enolates of Cyclohexanone Derivatives in DME

| Enolate | Metal | RX | Temp | k |
|---|---|---|---|---|
| XLV | Li | EtI | 0.0°[a] | $2.462 \times 10^{-4}$[b] |
| XLVI | Li | EtI | 0.0° | $3.618 \times 10^{-4}$[b] |
| XLV | K | n-BuBr | 29.95±0.05° | $3.718 \times 10^{-2}$[c] |
| XLVI | K | n-BuBr | 29.95±0.05° | $1.136 \times 10^{-2}$[c] |
| IX[d] | K | n-BuBr | 29.95±0.05° | $1.222 \times 10^{-2}$[c] |
| XLV | Li | EtI | 29.95±0.05° | $2.368 \times 10^{-3}$[b] |
| XLVII | Li | EtI | 0.0° | $4.099 \times 10^{-4}$[b] |
| XLVIII | Li | EtI | 0.0° | $0.781 \times 10^{-4}$[b] |
| XLV[e] | Li | EtI | 0.0° | $7.215 \times 10^{-4}$[b] |

[a] Temperature maintained by a crushed ice-water mixture.

[b] Pseudo-first-order rate constants in $sec^{-1}$.

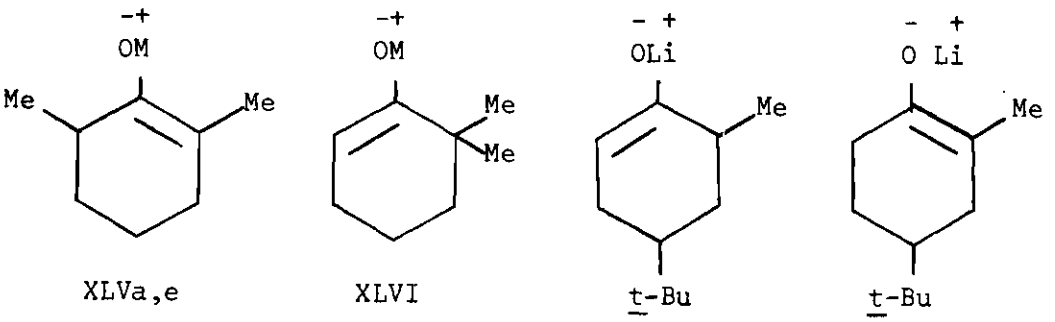
[c] Second order rate constants in liter/(mole x sec). Each value is an average of two independent determinations for all rate constants reported.

[d] Equilibrium mixture of enolates

[e] Solvent contained 10 per cent N,N-dimethylformamide.

The kinetic results demonstrate that the lithium enolate XLVI reacts faster than its isomer XLV with excess ethyl iodide in DME by a factor of 1.5. However, with the potassium enolates in DME and using n-butyl bromide as an alkylating agent, the order of reactivity is reversed and XLV reacts faster than XLVI by a factor of 3.3. In addition the less substituted enolate XLVII of cis-XI reacts faster than its counterpart by a factor of 5.2. (These values were calculated from data on kinetic

and equilibrium mixtures of lithium enolates of cis-XI.) In addition, the equilibrium mixture of potassium enolates of IX has about the same reactivity as does the potassium enolate XLVI.




XLVa,e XLVI t-Bu t-Bu

XLVIIa,e XLVIII

a = C-6 Me quasiaxial

e = C-6 Me quasiequatorial

The lithium enolates of IX are to be discussed later as a separate case because meaningful rate constants could not be obtained.

The enolate solutions were prepared by treating the ketones with trityl lithium or trityl potassium in DME, and these were assayed and the alkylation rates followed by acidimetry (see Chapter III). The specific alkylating agents were selected to give experimentally convenient alkylation rates. The calculated mean square pseudo-first-order rate constants recorded in Table 6 showed only minor variation for at least one (to two) half-lives. The second order rate constants are reported for the first 35 per cent of the reaction. The variation was generally less than 10 per cent; the standard deviation for each value is given in Appendix B. In all cases mono-C-alkylation was by far the predominant reaction pathway.

In order to test the relative reactivity of the lithium enolates of 2,2-dimethylcyclohexanone (X) and 2, 6-dimethylcyclohexanone with another alkylating agent, lithium enolates XLV and XLVI were alkylated with allyl bromide in DME at 0°. At convenient rates the reaction could not be run under pseudo-first-order conditions. The second order rate constants for each enolate decreased monotonously with time. The reactivity ratio of XLVI to XLV begins at about 1.7 and falls to about 1.3 as the reaction proceeds. At any rate the lithium enolate of 2,2-dimethylcyclohexanone is more reactive with allyl bromide (Figure 7).

With a given metal the rates of alkylation and, hence, the free energies of activation for alkylation with a particular alkyl halide are quite close for XLV and XLVI. In view of this, variations in ground state energy levels of the enolates could be partially responsible for the observed reversal in order of reactivity in going from lithium to potassium. Estimates of relative ground state stabilities of XLV and XLVI were obtained by treating a mixture of one equivalent each of VII and X with one equivalent of trityl lithium or trityl potassium in DME, allowing equilibrium to be established and quenching the mixture with acetic anhydride (49). VPC analysis of the enol acetate mixtures thus produced showed that for the lithium case the XLV/XLVI ratio was 70/30, while in the potassium case it was 45:55. Indeed, in each case there was a general correlation between enolate stability and reactivity in the alkylation reaction.

In Table 7 ground state energy levels of several lithium enolates are presented based on equilibrating mixtures of ketones or establishing

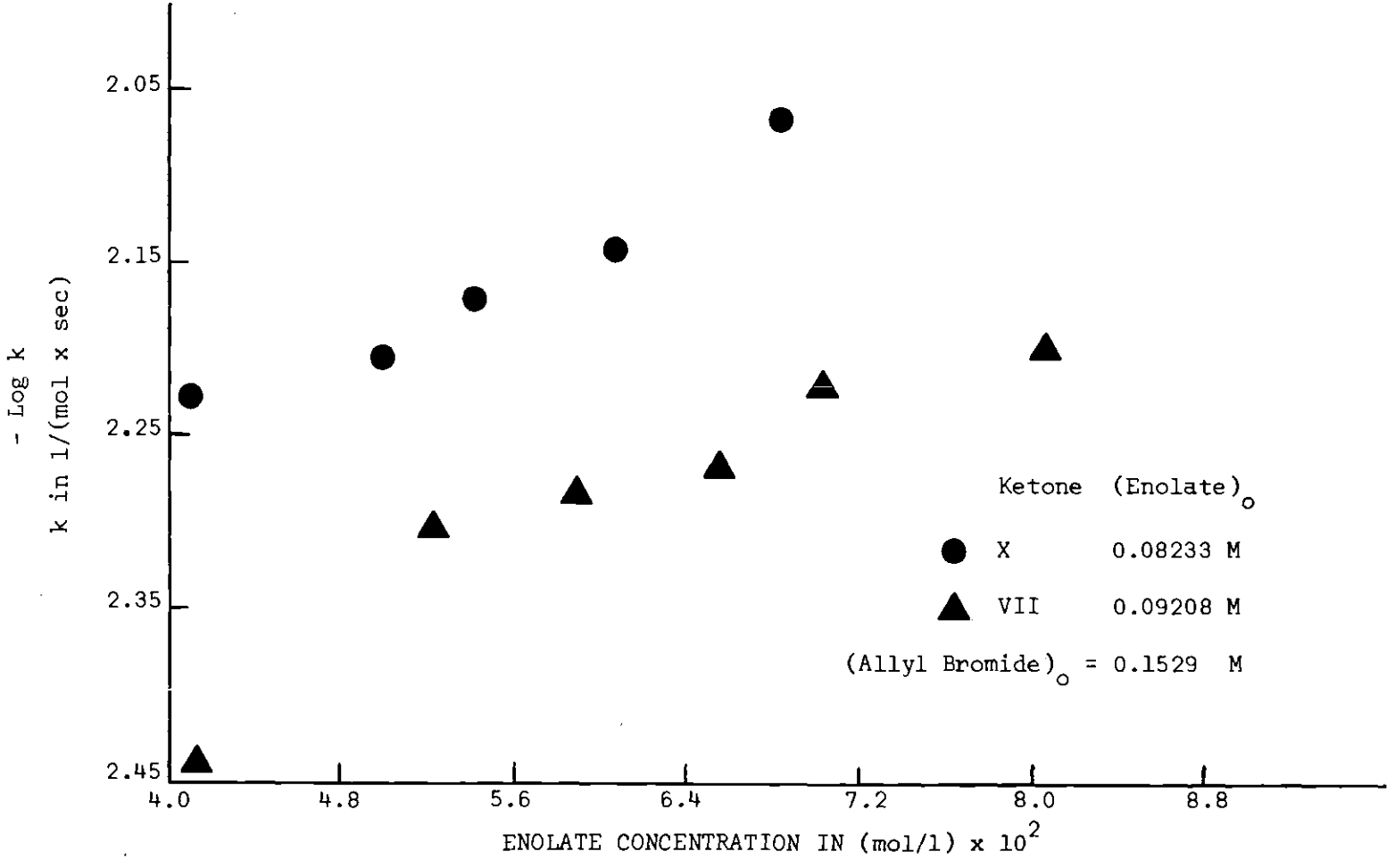



Figure 7. Rate Constants for Alkylation of 2,2- and 2,6-Dimethylcyclohexanone with Allyl Bromide in DME at 0° at Various Enolate Concentrations

equilibrium of the isomeric enolates from an unsymmetrical ketone as described in Chapter III.

Table 7. Relative Ground State Energies of Lithium Enolates of Cyclohexanone Derivatives in DME

| Enolate | Arbitrary Ground State Energy at 25° kcal/mol | Relative Reactivity in Ethylation with EtI at 0° |
|---|---|---|
| XLVIII | 0.00 | 1.00 |
| XLV | 0.81 | 3.15 |
| XLVI | 1.32 | 4.63 |
| XLVIIe | 1.25 | 5.24 |

The relative reactivity of the lithium enolates based on the results in Table 6 are included for comparison. Again the generalization holds that relatively high ground state energy corresponds to greater activity for lithium enolates in DME.

The activation parameters for the alkylation of XLV can be derived from the data in Table 6. The enthalpy of activation is 11.8 kcal/mol; $\underline{\Delta}F^{\neq}$ is 21.5 kcal/mol and $\underline{\Delta}S^{\neq}$ is -32.5 cal/°K. (These values would be considered normal (21)). The reaction exhibits a solvent effect with the rate increasing by a factor of 2.9 for a solvent containing 10 per cent N,N-dimethylformamide.

Returning to the surprisingly small difference in the alkylation rates of metal enolates of 2,2- (X) and 2,6-dimethylcyclohexanone (VII), it may be stated that the alkylation of a metal enolate of a cyclohexanone derivative can occur *via* a stereoelectronically controlled axial

attack or *via* a non-chair transition state which allows continuous p-orbital overlap (1). (This is shown graphically in Figure 11 discussed in connection with the stereochemical aspects of alkylation.) In a chair-axial alkylation of XLVI, there exists a 1,3-interaction between the approaching alkylating agent and a quasiaxial methyl group at C-2. Considering this factor alone, XLVI would be expected to be less reactive than XLV. It is true, however, that the difference might not be as large as expected. The solvent shell-quasiequatorial methyl interaction (61) in conformation XLVe causes the enolate anion to exist to a substantial degree (about 40 per cent for both the potassium (61) and the lithium enolate (reported here) in DME) in conformation XLVa having the C-2 methyl group quasiaxial. This species would also be relatively unreactive in a chair-axial alkylation, and its presence in equilibrium with XLVe would lower the over-all reactivity of XLV. Examination of models suggests that the steric factors that would be involved in a non-chair alkylation of both conformers of XLV and of XLVI are quite similar. Thus, if this pathway alone were involved in alkylations of XLV and XLVI, reaction rates for the two enolates would be expected to be very close.

At any rate for both metals the magnitude of the steric factor when a chair-axial alkylation is considered is quite small. This suggests that the geometry of the transition state for the alkylation closely resembles that of the metal enolate and that a transition state involving non-chair alkylation is readily accessible or actually preferred in these systems.

The reversal of reactivity* in changing the metal from lithium to potassium results from a combination of an enhanced nucleophilicity of carbon, a more favorable situation for chair-axial alkylation for XLV, and comparable ground state energy levels for XLV and XLVI in the potassium case. However, with lithium the first two factors noted above appear to be overshadowed by the higher ground state energy of XLVI so that it is more reactive than XLV. The influence of the methyl group on the double bond in affecting the relative reactivity of XLV and XLVI (XLVII and XLVIII also) is small; however, the rate enhancing electronic effect appears to be more important than its rate retarding steric effect, particularly in the potassium case.

Rates of Alkylation of Lithium Enolates of 2-Methylcyclohexanone (IX) and Cyclohexanone (XXXIII)

2-Methylcyclohexanone (IX) should be an excellent system for studying the rates of alkylation at specific α-positions in unsymmetrical ketones. The rate data, however, did not yield meaningful rate constants even under pseudo-first-order conditions. The situation was even further complicated with relatively reactive alkylating agents because pseudo-first-order conditions could not be used to yield conveniently measurable rates. In view of this, observations regarding rates of

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*The difference between ethyl iodide and n-butyl bromide could affect the order of reactivity. Since displacing bromide is generally more difficult than displacing iodide in alkylations, the transition state for alkylation via alkyl bromides may require a closer approach by the enolate anion than alkylation *via* alkyl iodides with a concomitant increase in product character. Any effect of this nature would enhance the relative reactivity of XLV.

alkylations of isomeric enolates of IX are based on average initial rates. Use of average initial rates causes few problems with equilibrium mixtures of lithium enolates of IX, but with kinetic mixtures the possibility for equilibration exists. During the first 20 per cent of the reaction of the kinetic mixture of lithium enolates of IX with methyl p-toluenesulfonate, no significant equilibration occurred. In addition, for all runs checked mono-C-alkylation is the major (virtually quantitative) pathway.

Table 8. Calculated Initial Rates of Alkylation of Lithium Enolates XXXIX and VI in 1,2-Dimethoxyethane[a]

| Alkylating Agents | Temp | $(\text{Enolate})_o$[b] | $(\text{RX})_o$[b] | AVERAGE INITIAL RATES $\bar{v}_{VI}$[c] | $\bar{v}_{XXXIX}$[c] | $\bar{v}_{XXXIX}/\bar{v}_{VI}$ |
|---|---|---|---|---|---|---|
| EtI | 25.10° | 0.03240 | 0.2240 | 2.92 | 5.13 | 1.75 |
| EtI | 0.0° | 0.06110 | 0.4980 | 2.51 | 5.85 | 2.33 |
| MeOTs | 25.10° | 0.04000 | 0.05470 | 2.59 | 4.19 | 1.62 |
| $C_3H_5Br$[d] | 0.0° | 0.07950 | 0.05162 | 4.00 | 26.78 | 6.69[c] |

[a]The rates are based on rates determined for kinetic and equilibrium mixtures of lithium enolates of IX. See Appendix C for complete data and Chapter III for the mathematical procedures.

[b]Initial molar concentration of reactants.

[c]Initial rate = decrease in enolate concentration over first 20 per cent reaction (based on the limiting reagent) in ((mol/l)/min) x $10^4$.

[d]Allyl bromide.

The data in Table 8 indicate that the more substituted enolate (XXXIX) of IX reacts with a variety of alkylating agents faster than does its isomer VI. (Complete data are given in Appendix C.) Generally, the rates are quite close except in the case of allyl bromide. The reason for the difference between allyl bromide and the other alkylating agents is not known. At any rate Table 8 shows that the alkylation rates of VI and XXXIX in DME are similar; the reactivity ratio is a function of alkylating agents and of temperature. The observed $v_{XXXIX}/v_{VI}$ ratios and the variation of this ratio with temperature in the ethyl iodide case indicate that the activation energy for alkylation of XXXIX is apparently less than that for VI. A combination of two factors is likely--a small rate enhancement by the C-2 methyl group on the double bond in XXXIX and/or the presence of a significant quantity of the less reactive conformer of VI.

Here, there must be other factors involved because the reactivity ratio is not in accord with ground state energy levels as was noted previously for the lithium enolates of cis-2-methyl-4-t-butylcyclohexanone (XI), 2,2- (X) and 2,6-dimethylcyclohexanone (VII). The data regarding XLV and XLVI, however, do suggest that steric and electronic factors should lead to a lower transition state energy for the more substituted than for the less substituted enolate of IX, but that the difference in the transition state energies for the two species would probably not be as large as the difference in ground state energies. A difference in the extent of association of the various lithium enolates may also, in part, account for the observed alkylation rate ratios.

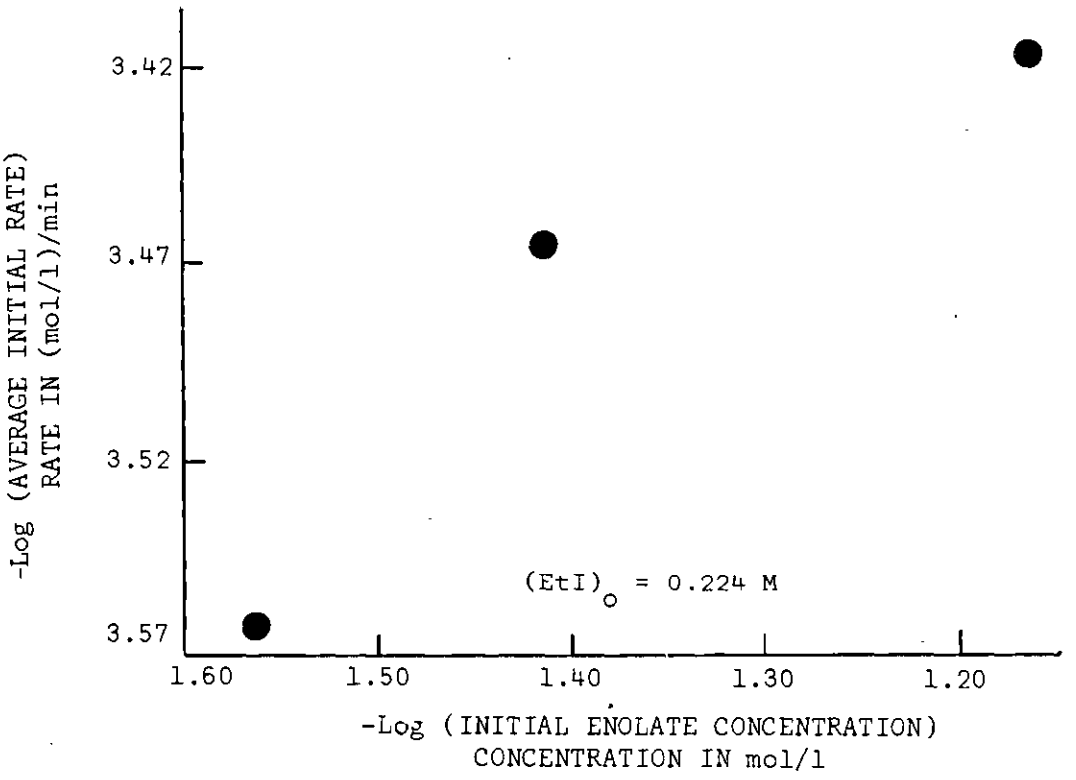



Figure 8. Order in Enolate for the Alkylation of the Kinetic Mixture of Lithium Enolates of IX with Ethyl Iodide in DME at 0°

In Figure 8 an order plot shows that the order with respect to lithium enolate is apparently a function of concentration and decreases with increasing concentration. Since association is ordinarily a function of concentration, it is reasonable that it is a significant factor in alkylation (19,20,23).

Because of the change in order with respect to concentration of the lithium enolates of IX, a study of cyclohexanone was prompted. Compound XXXIII offers a system which yields only one lithium enolate and would be expected to be sensitive to association. In Figure 9 an order plot is shown for the lithium enolate of cyclohexanone reacting

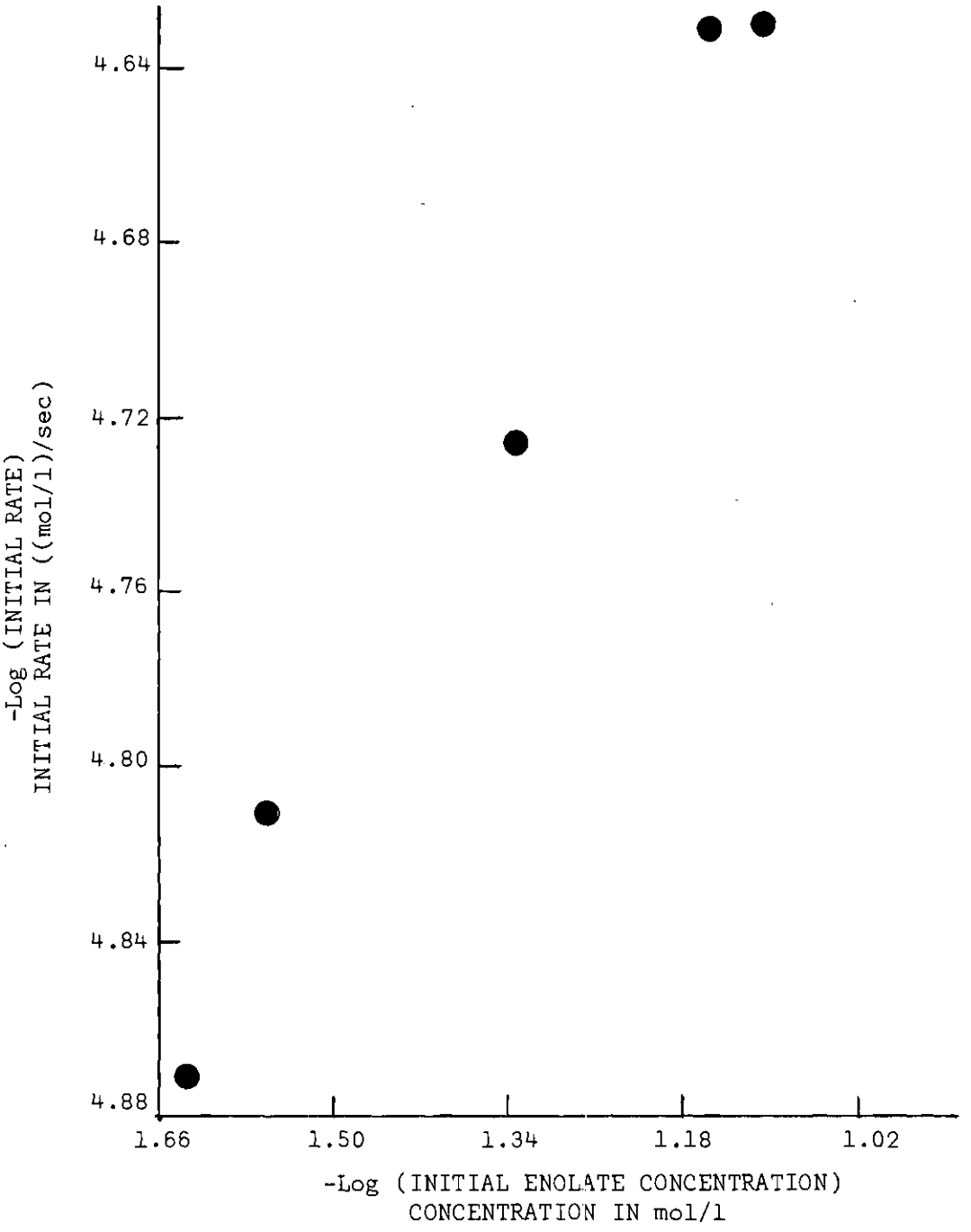



Figure 9. Order Plot for the Lithium Enolate of Cyclohexanone Reacting with Ethyl Iodide in DME at 0°

with ethyl iodide in DME at 0°. A curved line with decreasing slope with increasing concentration fits the data best. The order also is obviously significantly different from unity. For a given run the pseudo-first-order rate constants increase with decreasing concentration. A possible reason for the increase in pseudo-first-order constant would be a change in the amount of aggregation of the ion pairs representing the lithium enolate in DME solution. The data in Table 9 reflect the tendency for the pseudo-first-order rate constants to increase.

Table 9. Calculated Pseudo-first-order Rate Constants for the Alkylation of the Lithium Enolate of Cyclohexanone with Ethyl Iodide (0.5000 M) in DME at 0°

| Time[a] | Run I Enolate Conc.[b] | k[c] | Time[a] | Run II Enolate Conc.[b] | k[c] |
|---|---|---|---|---|---|
| 0 | 0.07981 | - | 0 | 0.02329 | - |
| 239 | 0.07325 | 3.12 | 240 | 0.01996 | 6.40 |
| 595 | 0.06498 | 3.27 | 359 | 0.01793 | 7.29 |
| 898 | 0.05778 | 3.47 | 501 | 0.01576 | 7.80 |
| 1196 | 0.05188 | 3.51 | 612 | 0.01346 | 8.96 |
| 1507 | 0.04547 | 3.66 | 902 | 0.00992 | 9.48 |
| 1805 | 0.03971 | 3.80 | 1211 | 0.00566 | 11.68 |
| 2100 | 0.03504 | 3.87 | | | |
| 2398 | 0.03024 | 4.00 | | | |
| 2992 | 0.02185 | 4.29 | | | |

[a] Sec. [b] mol/l. [c] $Sec^{-1} \times 10^{4}$.

Both runs recorded in Table 9 were followed for approximately two half-lives.

Aggregation would, of course, reduce the total enolate concentration by a factor, $\underline{\alpha}$, the association factor. Then, the rate = k (Enolate)/$\underline{\alpha}$ where $\underline{\alpha}$=1 at infinite dilution. The rates of alkylation at various values of enolate concentration were measured from the slope of the curve of concentration versus time for the first run in Table 9. The quantity k/$\underline{\alpha}$ was plotted against enolate concentration, and a value of k was determined by extrapolation to infinite dilution. The calculated values for $\underline{\alpha}$ to give a straight line over the reaction varied from 4.9 at 0.08M to 2.7 at 0.02 M. Essentially the same values may be obtained by plotting the calculated values of k versus concentration for all the runs made with XXXIII and extrapolating to zero concentration as illustrated in Figure 10. (Complete data concerning initial rates are given in Appendix D.) No association studies were performed to check the empirical association values, but Zook and Rellahan (23) observed similar behavior in the alkylation of the sodium enolate of butyrophenone in ether with ethyl bromide.

Another possible reason for increasing pseudo-first-order constants is catalysis by the reaction products similar to that observed by Zook and Gumby (19) in the ethylation of sodiobutyrophenone. The rates of ethylation of the kinetic mixture of lithium enolates from IX were run at several levels of free ketone concentration and are reported in Table 10. There is a slight increase in initial rate which can be observed by increasing the free ketone concentration from 0 to over 100 per cent of the initial enolate concentration.

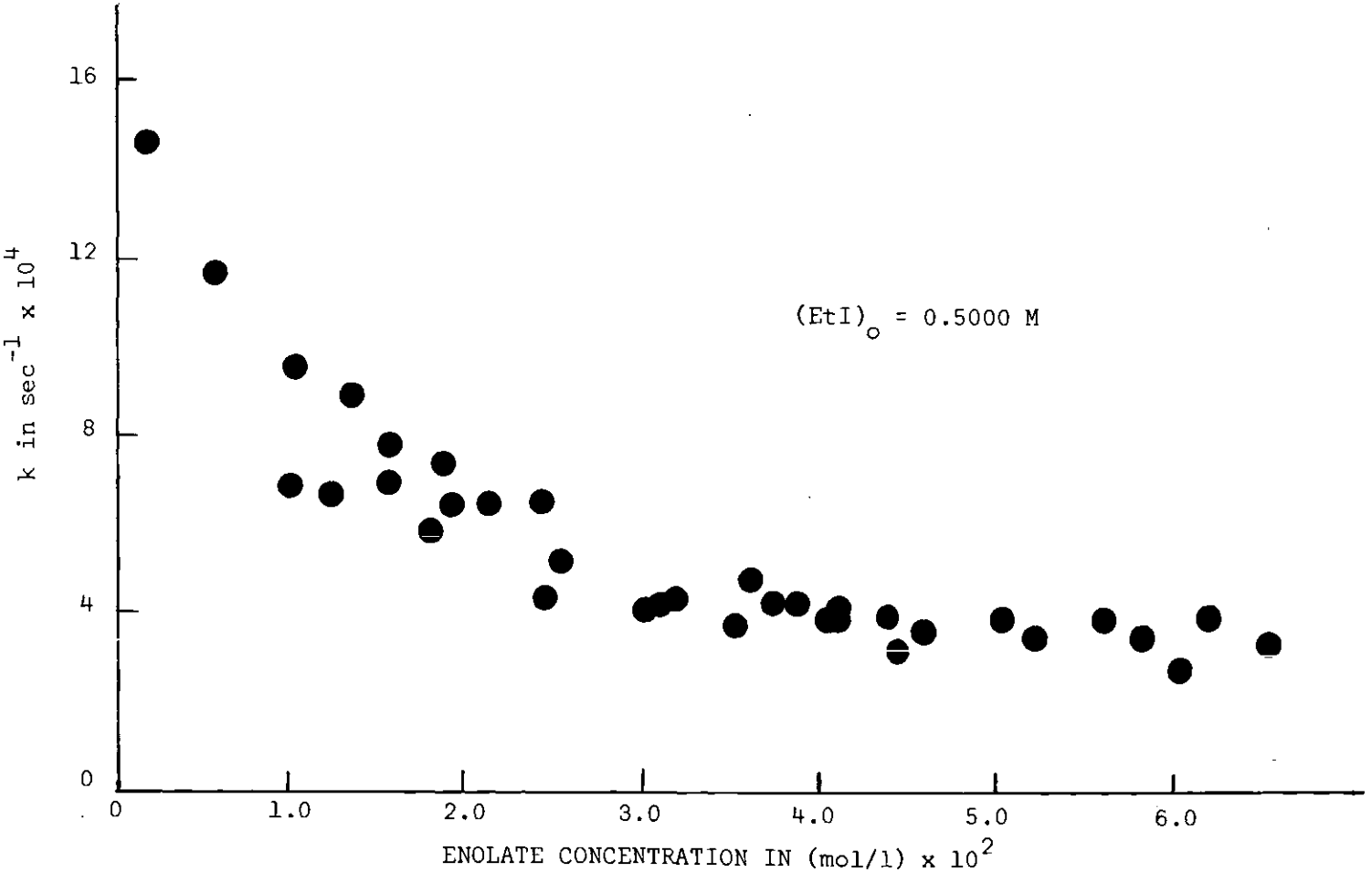



Figure 10. Calculated Pseudo-first-order Rate Constants for the Ethylation of the Lithium Enolate of Cyclohexanone in DME at 0°

Table 10. Variation in Initial Rate with Free Ketone Concentration in the Reaction of the Kinetic Mixture of the Lithium Enolates of 2-Methylcyclohexanone with Ethyl Iodide in DME at 0°

| $(Enolate)_o^a$ | $(EtI)_o^a$ | $(Ketone)_o^a$ | Initial Rate[b] |
|---|---|---|---|
| 0.054 | 0.500 | 0 | $3.00 \times 10^{-4}$ |
| 0.054 | 0.500 | 0.005 | $3.10 \pm 0.26 \times 10^{-4}$ |
| 0.054 | 0.500 | 0.065 | $3.35 \times 10^{-4}$ |

[a]Concentration in mol/l. [b](mol/l)/min

The statistical variation of the value listed for 10 per cent excess ketone is given on the basis of three independent trials. The slight autocatalytic effect is negligible in comparison to the increase in pseudo-first-order constant observed for the lithium enolate of cyclohexanone.

Several attempts were made to fit the data for the ethylation of cyclohexanone in DME at 0° to model systems. The form of the data suggests a mechanism involving association of ion pairs with one or more reactive species in equilibrium with higher aggregates, illustrated in Equation 7.

Models assuming the monomer to be the reactive species and all the equilibrium constants in Equation 7 to be equal (78) failed to fit the system; a model assuming the dissociation constants to be proportional to the number of monomer units in the agglomerate (79) did not improve the situation.

$$(LiE)_n \overset{K_{n-1}}{\rightleftharpoons} (LiE)_{n-1} + LiE \qquad (7)$$

$$\vdots$$

$$(LiE)_2 \overset{K_1}{\rightleftharpoons} LiE + LiE$$

$$(LiE)_x \xrightarrow{RX} \text{Products} + (LiE)_{x-1}$$

This type of mechanism, however, best fits the observed kinetics, but the monomer may not be the only reactive species. In addition, the inter-relationships among the various equilibria may be much more complicated than suggested by the Streitwieser (78,79) models.

A mechanism involving the free enolate anion is considered unlikely based on an experiment on the lithium enolate of cyclohexanone run in the presence of lithium perchlorate. This salt should be at least as dissociated in DME as the lithium enolate of XXXIII. Accordingly, a large rate decrease would be expected in the presence of appreciable quantities of lithium perchlorate if the free anion is directly involved in determining the alkylation rate of the lithium enolate of XXXIII. The initial rate of ethylation measured at an initial enolate concentration of 0.03669 M in the presence of 0.053 M lithium perchlorate was $1.549 \times 10^{-5}$ (mol/l)/sec; the value expected based on Figure 10 is $1.54 \times 10^{-5}$ (mol/l)/sec. Based on Figure 9 the value observed in the presence of lithium perchlorate is about 10 per cent below the expected value. Thus, the free anion is not a significant factor.

## Stereochemistry of Alkylation of Metal Enolates

### Methylation of the Lithium Enolate of 4-t-Butylcyclohexanone

From kinetic results it could be postulated based on the absence of a significant steric rate retardation expected in the alkylation of 2,2-dimethylcyclohexanone that either bond formation was not important in the transition state for alkylation or that a non-chair path for alkylation was readily available, or both. The second postulate prompted the study of the stereochemistry of alkylation of rigid systems which can maintain stereochemical integrity after the reaction. The first system selected was 4-t-butylcyclohexanone (XLIX) and the methylation of the lithium enolate produced by trityl lithium in DME with methyl iodide.

As pointed out earlier, the enolate anion for stereoelectronic reasons must be attacked by the alkylating agent at a particular α-carbon from directions perpendicular (26) to the plane containing the α-carbon and the original carbonyl group. This is illustrated in Figure 11, and the two possible modes of perpendicular attack are labeled chair on non-chair depending on the conformation of the alkylated product that is initially generated. If alkylation occurs along the chair path, the resulting product assumes the chair conformation with the new alkyl group in an axial position. If the reactant approaches perpendicularly from the opposite direction, the product is constrained to adopt a twistboat conformation B. Subsequent conformational change leads to the cis-diequatorial product C. Since it is generally assumed that a chair transition state will have lower energy than its twist-boat counterpart

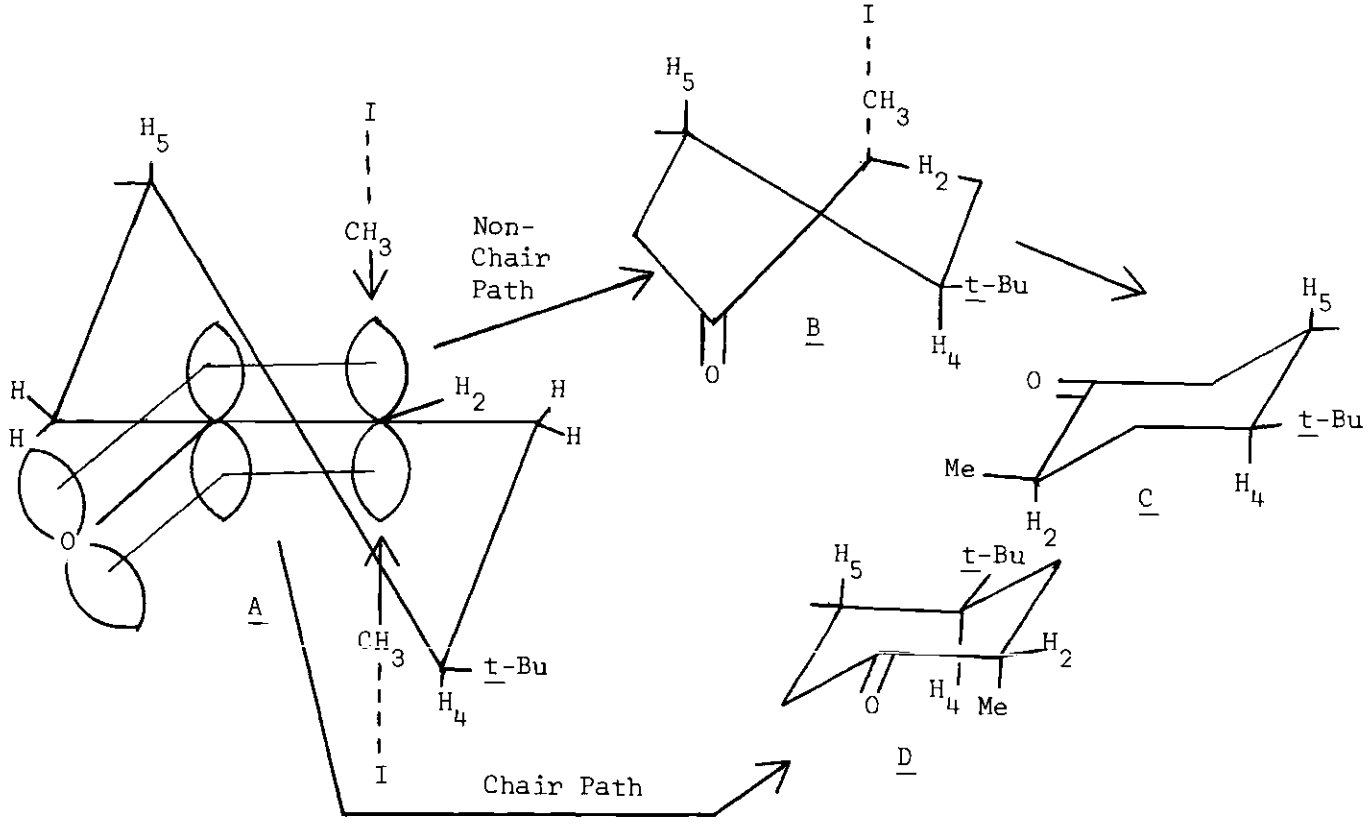
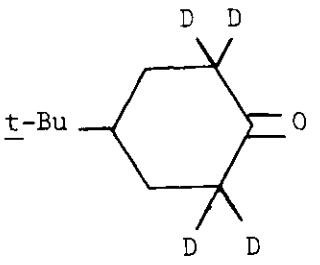



Figure 11. Alkylation Pathways for the Lithium Enolate of 4-t-Butylcyclohexanone

(80), alkylation *via* the chair path should be the favored process based on steric interactions in the product and in the absence of severe opposing steric and conformational interactions in the transition state.

Methylation of the lithium enolate of 4-t-butylcyclohexanone (XLIX) produced a mixture of isomers, 45 per cent trans-XI (chair path) and 55 per cent cis-XI (non-chair path). This represents the minimum trans-XI produced because of possible equilibration during or after the reaction. House, *et al.* (30), demonstrated the absence of equilibration of the isomers of the 2-alkyl-4-t-butylcyclohexanones during the reaction by alkylating enolates derived from XLIX and its tetradeuteroderivative L with ethyl iodide to form primarily $d_0$ and $d_3$ species.

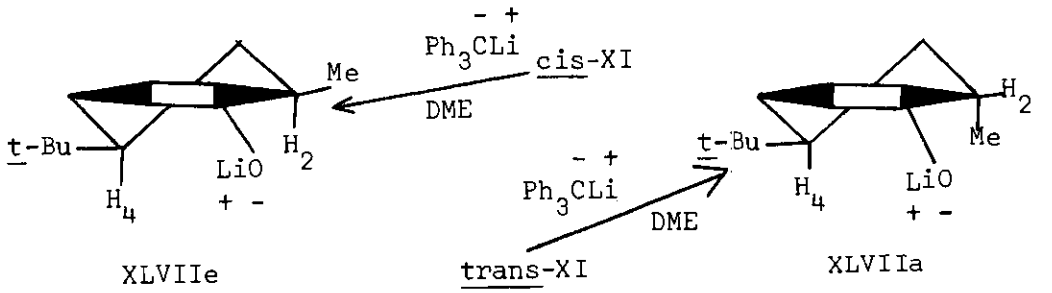



L

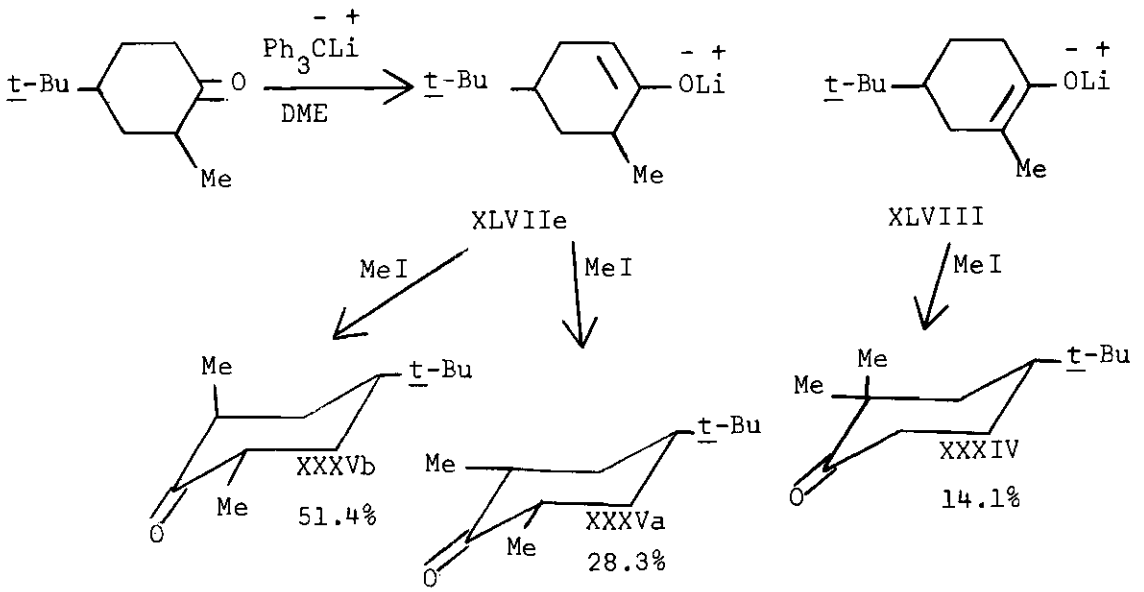
Work-up of the methylated product (see Chapter III) in deuterium oxide produced negligible deuterium incorporation for isomers of XI; therefore, equilibration during work-up was insignificant. At any rate there is a non-chair path readily accessible for the methylation of the lithium enolate of XLIX. The approximately one-to-one ratio of cis- and trans-products indicates that the transition state resembles the enolate anion because product interactions predict a very different course (80).

Methylation of the Less Substituted Lithium Enolates of 2-Methyl-4-t-butylcyclohexanone

The ketone, 2-methyl-4-t-butylcyclohexanone, provides two less substituted enolate anions depending upon the starting isomer of XI used.




Methylation of the kinetic mixture of lithium enolates from 93 per cent cis-XI in DME produced a mixture of ketones in which the 2,6-dialkyl




product derived from a chair path (XXXVb) predominated by a factor of

1.8 with respect to its non-chair counterpart XXXVa (see Chapter III). Placing an alkyl group in a quasiequatorial orientation at C-6 in lithium enolate A in Figure 11 would produce an interaction with the solvent shell about the oxygen-metal bond in the enolate anion. Even though the rigid system cannot undergo a conformational change with the facility that the less substituted lithium enolate of IX can, the enolate anion will realign to account for this interaction moving the alkyl group into a position in which the interactions in the non-chair path are increased (illustrated in Figure 12).

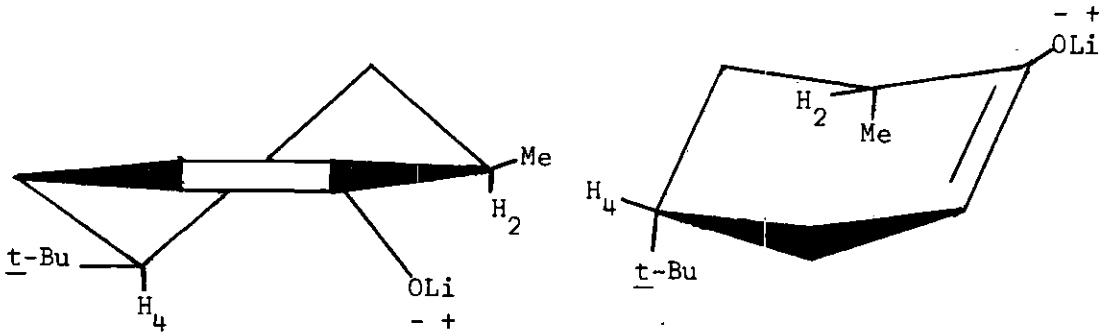
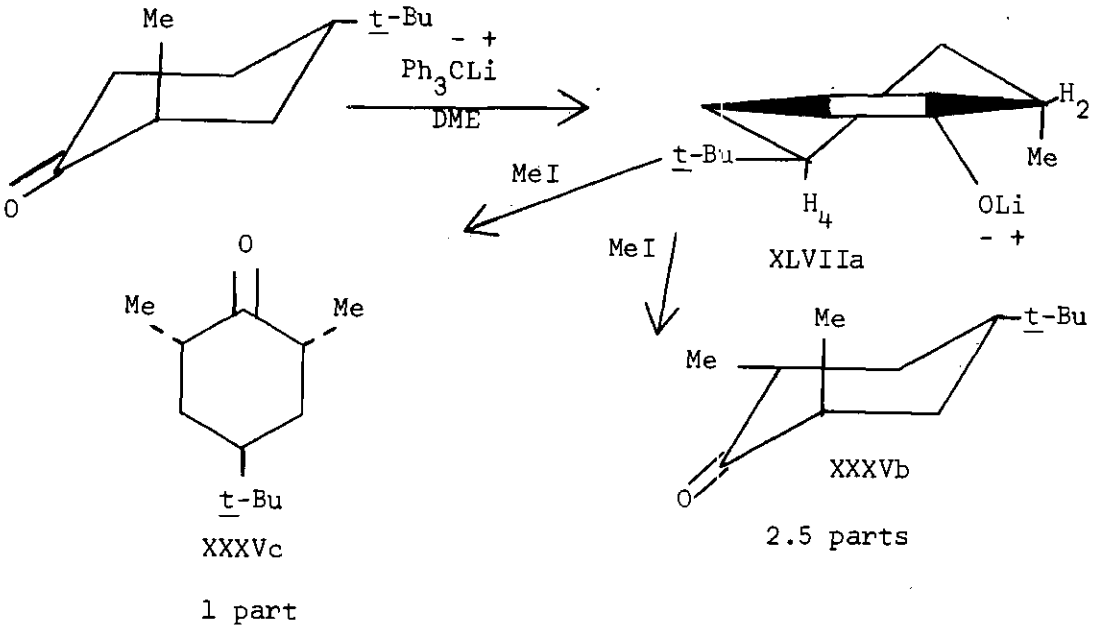



Figure 12. Skewing of the Lithium Enolate XLVIIe as a Result of Solvent Shell Interaction

In the limit this realignment would result in a half-boat conformation for the enolate anion XLVIIe. Perpendicular attack along the chair pathway is still no more hindered in the skewed half-chair conformation than before, whereas the non-chair pathway is more hindered than the lithium enolate of 4-t-butylcyclohexanone.

Methylation of the less substituted enolate (XLVIIa) from trans-XI results in predominant alkylation *via* a non-chair path since XXXVb is the major product. The presence of an axial methyl group at C-2 hinders chair alkylation, but still a mixture is produced. The

methylation results for the less substituted enolates from cis- and trans-XI may be rationally explained on the basis that the transition state for alkylation resembles the enolate anion and that factors in the initially formed product are not controlling.




Trideuteromethylation of the More Substituted Enolate (XLVIII) from 2-Methyl-4-t-butylcyclohexanone

The obvious method to choose to eliminate any possibility of stereochemical interconversion of products is to produce an α,α-dialkyl product from a rigid system. Since methylation of XLVIII would produce 2,2-dimethyl-4-t-butylcyclohexanone (XXXIV), a compound which could not be analyzed for direction of alkylation, trideuteromethyl iodide (81) was selected for the alkylating agent. Alkylating XLVIII with methyl

iodide-$d_3$* produced a product in which the methyl-$d_3$ group was introduced axially with a preference of 2.4 to 1. The orientation of the methyl group was assigned on the basis of nmr spectroscopy. The data in Table 11 demonstrate that methyl groups trans (presumably axial) to the t-butyl group absorb down-field from methyl groups cis (presumably equatorial) to the t-butyl moiety.

Table 11. NMR Spectra of 4-t-Butylcyclohexanone Derivatives and 2,6-Dimethylcyclohexanone

| Ketone | Chemical Shift α-Me in $CCl_4$ (ppm) | Chemical Shift α-Me in $C_6H_6$ (ppm) | Change in δ |
|---|---|---|---|
| cis-XI[a] | 0.93 | 1.01 | -0.08 |
| trans-XI | 1.10 | 1.01 | +0.09 |
| XXXIV[a] | 1.00 | 1.11 | -0.11[a] |
| | 1.13 | 0.94 | +0.19[a] |
| XXXVa | 0.96 | 1.00 | -0.04 |
| XXXVb | 0.97 | - | - |
| | 1.13 | - | - |
| cis-VII[b] | 0.93 | - | - |
| trans-VII[b] | 0.93 | - | - |
| | 1.03 | - | - |

[a]Reported in Reference 62. [b]Reported in Reference 12.

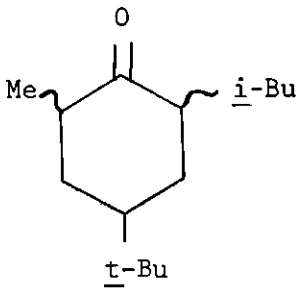
This is clearly demonstrated for trans-XI and trans-VII and by analogy for XXXVb. In addition, the change in chemical shift for cis-XI in going from carbon tetrachloride to benzene is that expected for an

*Diaprep kindly supplied the trideuteromethyl iodide used in these experiments.

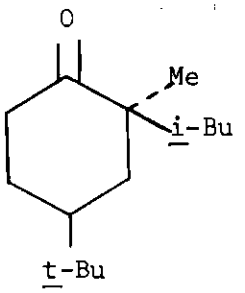
equatorial methyl group α to a carbonyl group (82). The change in chemical shift for trans-XI is consistent with an axial orientation (82). Unless XXXIV is in a twist conformation, the low-field absorption is properly assigned to the axial methyl group. On trideuteromethylation of XLVIII the absorption at 1.13 ppm ($CCl_4$) diminished in comparison with that for XXXIV, indicating that the major fraction of the methyl-$d_3$ group had been introduced in an axial orientation.

Isobutylation of the More Substituted Metal Enolate (XLVIII) of 2-Methyl-4-t-butylcyclohexanone

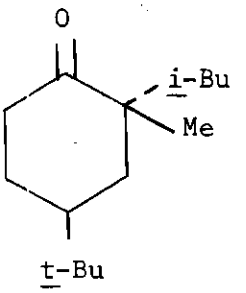
Conia and Briet (35, 62) reported that isobutylation of the sodium enolate of XI in benzene with isobutyl iodide produced 12 per cent XXXVIII, 52 per cent XXXVIIa, and 36 per cent XXXVIIb.




XXXVIII



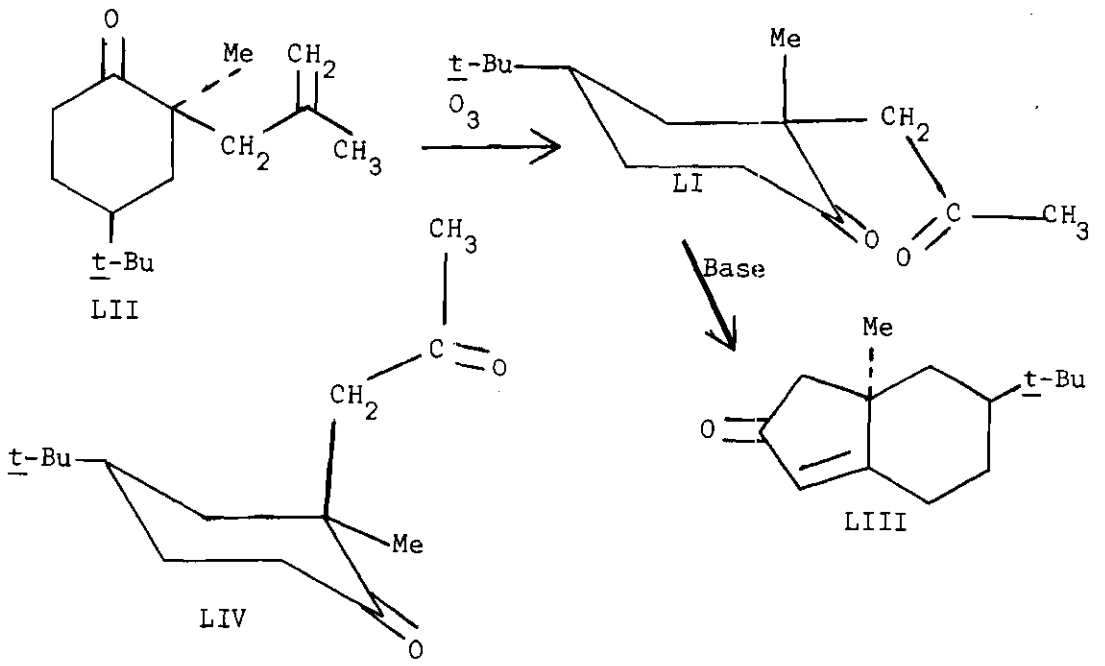

XXXVIIa




XXXVIIb

These configurations were assigned on the basis that the rate of cyclization of cis-2-(2'-oxopropyl)-2-methyl-4-t-butylcyclohexanone (LI) prepared from the corresponding methallyl compound LII (related to XXXVIIa by hydrogenation) was much faster and produced the corresponding bicyclononenone (LIII) in higher yield than did dione LIV related to XXXVIIb. The argument is that LI with the acetonyl group equatorial

should cyclize faster than LIV with this group axial, and this observation is certainly reasonable.




However, to explain the nmr spectra and solvent shifts it must be assumed that compounds XXXVIIa and XXXVIIb are in twist-boat conformations (62).

Alkylating the equilibrium mixture of potassium enolates of XI in DME with isobutyl iodide yielded 54 per cent XXXVIIa, 38 per cent XXXVIIb, and 8 per cent XXXVIII. Isobutylation of the equilibrium mixture of lithium enolates of XI yielded 55 per cent XXXVIIa, 33 per cent XXXVIIb and 12 per cent XXXVIII. The values are not very different from the ratios determined by Conia and Briet (35). These values indicate a preference for non-chair alkylation with isobutyl iodide by a factor of

1.7; however, trideuteromethylation indicated a preference for chair alkylation. Since the ethylation (30) and methylation of 4-t-butylcyclohexanone gave similar results as did the ethylation and trideuteromethylation of 4α-methyl-19-nortestosterone at C-4 (81), isobutylation and trideuteromethylation could be expected to give similar results neglecting the "2-alkyl ketone effect" (83).* This interaction, however, is much smaller than the interactions that would be introduced in a skew-boat conformation (86).

Based on results from this research the exact configuration of XXXVIIa and XXXVIIb cannot be assigned unequivocally,** and it must be emphasized that Conia's assignment may be correct. The other evidence relating to the stereochemistry comes from photochemical experiments performed in cyclohexane. When XXXVIIa is photolyzed in cyclohexane (even in the presence of up to 0.5 M 1,3-pentadiene), it readily isomerizes to XXXVIIb. When XXXVIIb is photolyzed under similar conditions, a slow conversion to 2-methyl-4-t-butylcyclohexanone *via* a Norrish Type II cleavage results (87). Turro and Weiss (87) observed that trans-2-propyl-4-t-butylcyclohexanone rearranges to cis-2-propyl-4-t-butylcyclohexanone on photolysis in cyclohexane. They also reported that the cis compound yields XI much more efficiently than does the trans compound *via* a Norrish Type II process, but they observed that

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*This effect amounts to about 0.7 kcal/mol for an ethyl group (84, 85) and should be similar for an isobutyl group.

**Attempts to prepare a crystalline bromo-derivative from LIII for X-ray analysis failed.

the isomerization of trans- to cis-2-propyl-4-t-butylcyclohexanone was strongly quenched by piperylene. These observations correlate with a configurational assignment for XXXVIIa and XXXVIIb opposite to that proposed by Conia (62).

Because the stereochemistry could also affect the efficiency of the McLafferty rearrangement, mass spectra were obtained on XXXVIIa and XXXVIIb. Unfortunately, loss of isobutylene *via* a McLafferty rearrangement with a loss of 56 mass units coincided with other cleavage patterns that result in a loss of 56 mass units as shown in Figure 13. Of course, Mode A corresponds to the McLafferty rearrangement. Modes B and C are other avenues for loss of 56 mass units. Mode C is postulated because a significant M - 56 peak is observed in the mass spectrum of 2,6-dimethyl-4-t-butylcyclohexanone where Mode B does not result in a loss of 56 mass units. That the McLafferty rearrangement is occurring is indicated by the fact that the molecular ion (m/e 224) in the mass spectra of both XXXVIIa and XXXVIIb has a very low intensity. All other alkylated 4-t-butylcyclohexanone derivatives that have been studied show a strong molecular ion in the mass spectrum.

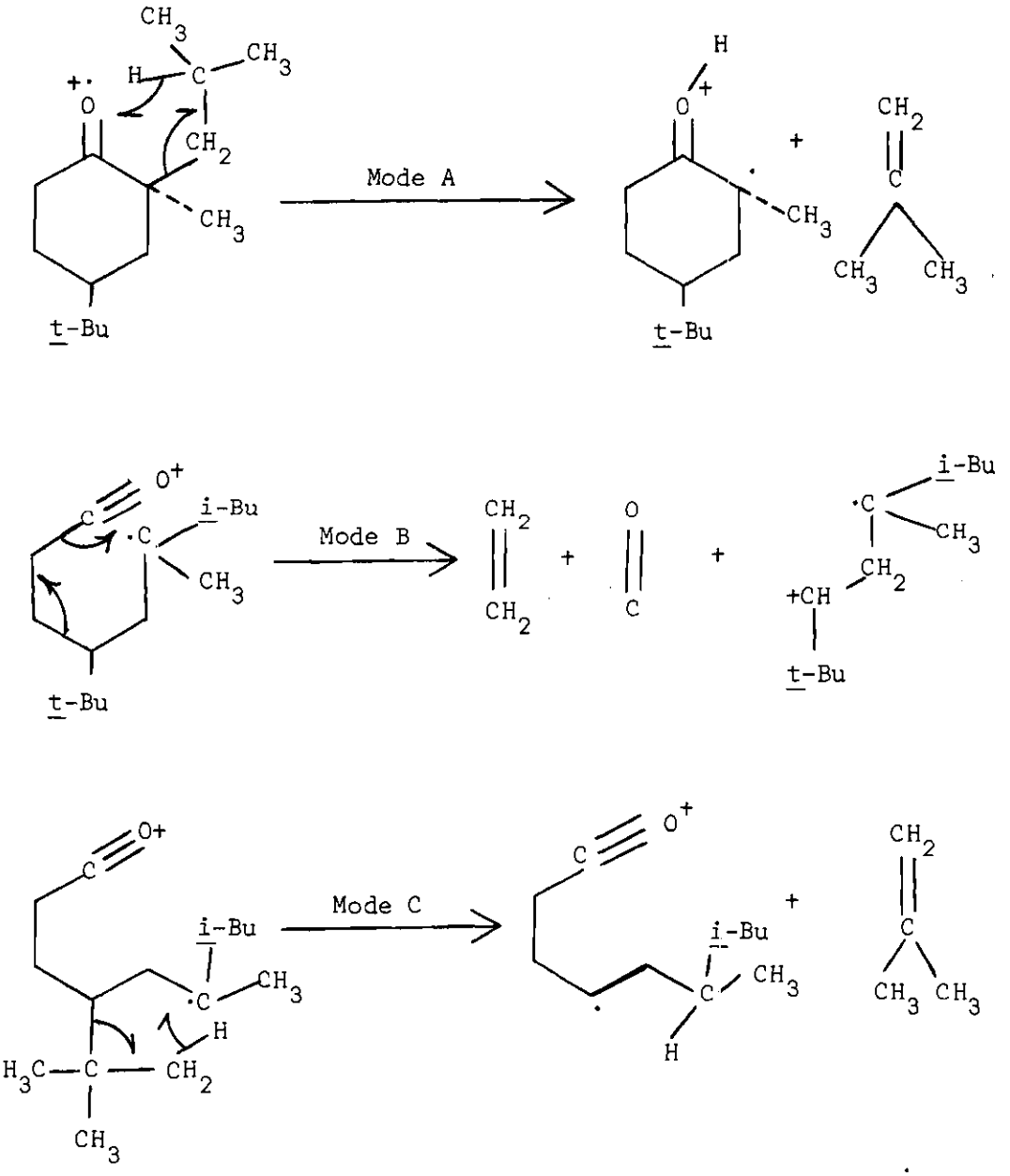


Figure 13. Possible Cleavage Patterns for 2-Isobutyl-2-methylcyclohexanone

The postulated preference* for axial or chair alkylation in the trideuteromethylation and isobutylation of the more substituted lithium enolate (XLVIII) from XI in light of the fact that essentially no difference is observed with the lithium enolate of 4-t-butylcyclohexanone is difficult to explain. For some reason the transition state for alkylation of XLVIII with trideuteromethyl iodide has more product character than the transition state for alkylation of 4-t-butylcyclohexanone with methyl iodide or ethyl iodide (30) in DME. A modest difference, 0.52 kcal/mol in the trideuteromethylation and less in the isobutylation, in activation energy for the two possible alkylation pathways is enough to account for the preference for chair-axial alkylation of XLVIII. Steric crowding in the transition state by the methyl group on the double bond in XLVIII could require closer approach to the

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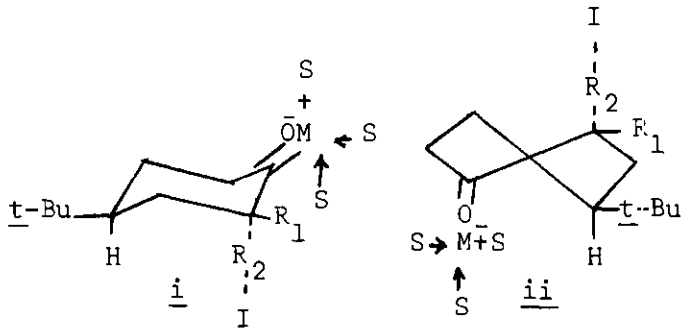
*A product argument has been used to predict a predominant non-chair alkylation for isobutylation of the sodium enolate XLVIII in benzene with isobutyl iodide.




It may be argued (30) that the chair path is disfavored by a nonbonding steric interaction in the transition state between equatorial 2 substituent (Me in structure i) and the solvated metal-oxygen bond. By assuming a geometry approaching the twist-boat (i.e., ii) the stipulated interaction can be reduced. The structure ii would lead to the observed preponderant product.

alkylating agent in the transition state for alkylation of XLVIII resulting in greater product character. Another possibility is that a small conformational change induced by the interaction between the C-2 methyl group and the cation solvent shell makes the attack of the alkylating agent *via* the non-chair pathway less favorable. This means that the eclipsed interaction (or torsional strain (88)) between the newly-forming bond and the appropriate C-3 proton (Figure 11) becomes greater than the axial-axial type steric interactions between the quasi-axial hydrogen at C-6 and the axial hydrogen at C-4 which are encountered for alkylation *via* a chair path.

# CHAPTER V

# CONCLUSIONS AND RECOMMENDATIONS

## Conclusions

Trityl lithium exhibits significant selectivity in abstracting the proton from the less substituted position of unsymmetrical ketones such as 2-methylcyclohexanone and cis-2-methyl-4-t-butylcyclohexanone in 1,2-dimethoxyethane. Trityl lithium, as well as trityl potassium, removes axial α-protons much faster than equatorial α-protons as shown by complete stereoselective formation of the less substituted enolate from trans-2-methyl-4-t-butylcyclohexanone in DME. Lithium enolates generated under kinetic conditions can be alkylated with many alkyl halides to give good yields of monoalkylated products in the same ratio in which the enolate anions are generated.

Reductive alkylation employing lithium in liquid ammonia provides a convenient means of synthesizing selectively alkylated cyclohexanone derivatives in cases where the necessary enones or α-haloketones are available. It provides distinct advantages over direct base-catalyzed alkylations of unsymmetrical ketones since such methods generally lead to mixtures of difficultly separable monoalkylation products as well as extensive di- and polyalkylation. This is the first example of an alkylation of the 3-alkylcyclohexanone system selectively *via* the $\Delta^{1(2)}$-enolate. The complete reduction of β-unsubstituted, α,β-unsaturated cyclohexanone derivatives requires one equivalent of an added proton

donor such as water or t-butyl alcohol.

Kinetics of ethylation of various cyclohexanones in DME indicates that ground state energy levels are a significant factor in determining alkylation rates in systems of comparable aggregation. The rate of ethylation of the lithium enolate of 2,2-dimethylcyclohexanone is faster than that of 2,6-dimethylcyclohexanone showing that steric interactions in the product are not controlling the energy of the transition state. The mechanism of alkylation consistent with all the observed kinetics is one involving reactive ion-pair species (one or more) in equilibrium with an unreactive aggregate. The free enolate anion is not a significant factor in the alkylation of lithium enolates of cyclohexanone derivatives with alkyl halides in DME.

Alkylation of 4-t-butylcyclohexanone and derivatives in DME demonstrates that chair and non-chair pathways for alkylation are both readily accessible. The transition state for alkylation resembles the enolate anion and the interactions in the latter are more important than interactions in the product in controlling the rate and stereochemistry of alkylation.

## Recommendations

A series of triphenylmethane derivatives, such as p-$CH_3$, p-$OCH_3$, p-$CF_3$, and p-phenyl derivatives, should be prepared, converted to the corresponding lithio-derivative, and reacted with unsymmetrical ketones to ascertain the steric and electronic factors that control selectivity in proton removal by trityl bases. Another aspect of lithium enolate chemistry that should be investigated is the conversion by trityl bases

of cyclohexenone derivatives, such as cholestenone and 10-methyl-$\Delta^{1(9)}$-octalone-2, to kinetic mixtures of lithium enolates with abstraction of a proton at C-2 and subsequent alkylation. Finally, a crystalline derivative of cis- or trans-2-isobutyl-2-methyl-4-t-butylcyclohexanone or a related compound should be prepared for X-ray analysis to establish definitely the configuration of one of the isomers.

# APPENDICES

# APPENDIX A

## ENOL ACETATES PRODUCED FROM KINETIC MIXTURES OF METAL ENOLATES OF KNOWN MIXTURES OF CIS- AND TRANS-2-METHYL-4-T-BUTYLCYCLOHEXANONE

| Fraction cis-XI % | Metal | XXIII % | XXIV % |
|---|---|---|---|
| 93 | Li | 87 | 13 |
| 93 | K | 70.5 | 29.5 |
| 25 | K | 97 | 3 |

# APPENDIX B

## RATE CONSTANTS FOR ALKYLATION OF METAL ENOLATES OF 2-METHYLCYCLOHEXANONE (IX), 2,2- (X), 2,6-DIMETHYLCYCLOHEXANONE (VII) AND CIS-2-METHYL-4-T-BUTYLCYCLOHEXANONE IN 1,2-DIMETHOXYETHANE

| Ketone | Metal | Alkylating Agent | $(Enolate)_o$[a] | $(RX)_o$[b] | Temperature | k[c] |
|---|---|---|---|---|---|---|
| X | Li | EtI | 5.835 | 0.5000 | 0.0°[d] | 3.590±0.283 |
| X | Li | EtI | 7.578 | 0.5000 | 0.0° | 3.646±0.095 |
| VII | Li | EtI | 5.398 | 0.5000 | 0.0° | 2.429±0.110 |
| VII | Li | EtI | 4.670 | 0.5000 | 0.0° | 2.495±0.244 |
| XI[e] | Li | EtI | 2.670 | 0.5000 | 0.0° | 3.920±0.293 |
| XI[e] | Li | EtI | 3.555 | 0.5000 | 0.0° | 3.349±0.639 |
| XI[f] | Li | EtI | 6.761 | 0.5000 | 0.0° | 1.012±0.057 |
| XI[f] | Li | EtI | 3.206 | 0.5000 | 0.0° | 1.243±0.105 |
| VII | Li | EtI | 7.320 | 0.5000 | 29.95° | 22.21 ±1.740 |
| VII | Li | EtI | 3.777 | 0.5000 | 29.95° | 25.14 ±1.340 |
| VII[g] | Li | EtI | 5.538 | 0.5000 | 0.0° | 7.215±0.422 |
| VII | K | n-BuBr | 4.912 | 0.07964 | 29.95° | 3.866±0.343[h] |
| VII | K | n-BuBr | 4.462 | 0.07964 | 29.95° | 3.571±0.195[h] |
| X | K | n-BuBr | 4.658 | 0.07964 | 29.95° | 1.266±0.159[h] |
| X | K | n-BuBr | 4.716 | 0.07964 | 29.95° | 1.005±0.064[h] |
| IX[j] | K | n-BuBr | 4.037 | 0.07964 | 29.95° | 1.241±0.085[h] |
| IX[j] | K | n-BuBr | 4.032 | 0.07964 | 29.95° | 1.203±0.038[h] |

[a]Initial concentration of enolate in (mol/l) x $10^2$. [b]Initial molar concentration of alkylating agent. [c]Pseudo-first-order rate constant in $sec^{-1}$ x $10^4$. [d]Temperature maintained by a crushed ice/water mixture. [e]Kinetic mixture of lithium enolates consisting of 87 per cent XLVII and 13 per cent XLVIII. [f]Equilibrium mixture of lithium enolates consisting of 89 per cent XLVIII and 11 per cent XLVII. [g]Solvent contained 10 per cent N,N-dimethylformamide. [h]Second order rate constants in (l/(mol x sec)) x $10^2$ based on the first 35 per cent of the reaction. [j]Equilibrium mixture of potassium enolates.

# APPENDIX C

## INITIAL RATES OF ALKYLATION OF LITHIUM ENOLATES OF 2-METHYLCYCLOHEXANONE (IX)

| Enolate Type | RX[a] | $(Enolate)_o$[b] | $(RX)_o$[c] | Temperature | $\underline{v}$[d] |
|---|---|---|---|---|---|
| $Eqm_f$[e] | MeOTs | 0.04003 | 0.05470 | 25.10° | 4.02 |
| Kin[f] | MeOTs | 0.04256 | 0.05588 | 25.10° | 2.78 |
| Kin | MeOTs | 0.06288 | 0.05487 | 25.10° | 4.82 |
| Kin | MeOTs | 0.04601 | 0.05376 | 25.10° | 2.88 |
| Eqm | EtI | 0.0324 | 0.224 | 25.10° | 4.91 |
| Kin | EtI | 0.0384 | 0.224 | 25.10° | 3.43 |
| Kin | EtI | 0.0691 | 0.224 | 25.10° | 3.83 |
| Kin | EtI | 0.0274 | 0.224 | 25.10° | 2.74 |
| Eqm | $C_3H_5Br$[g] | 0.0728 | 0.0530 | 0.0 ° | 24.50 |
| Eqm | $C_3H_5Br$ | 0.0709 | 0.0530 | 0.0 ° | 23.80 |
| Kin | $C_3H_5Br$ | 0.0795 | 0.0516 | 0.0 ° | 7.20 |
| Kin | $C_3H_5Br$ | 0.0600 | 0.0493 | 0.0 ° | 5.44 |
| Eqm | EtI | 0.06115 | 0.5005 | 0.0 ° | 5.52 |
| Kin | EtI | 0.06107 | 0.5006 | 0.0 ° | 2.98 |
| Kin | EtI | 0.05493 | 0.4999 | 0.0 ° | 3.47 |
| $Kin_h$ | EtI | 0.04800 | 0.5015 | 0.0 ° | 2.86 |
| Kin[h] | EtI | 0.05376 | 0.5000 | 0.0 ° | 3.00 |
| Kin[j] | EtI | 0.05315 | 0.5000 | 0.0 ° | 3.35 |

[a]RX = alkylating agent. [b]Initial molar concentration of the enolate. [c]Initial molar concentration of the alkylating agent. [d]Average initial alkylation rate in ((mol/l)/min) x $10^4$. [e]Equilibrium or thermodynamic. [f]Kinetic. [g]Allyl bromide. [h]Contained no free ketone at the beginning of the reaction. [j]Contained 0.065 M free ketone at the beginning of the reaction.

# APPENDIX D

## AVERAGE INITIAL RATES OF ETHYLATION OF THE LITHIUM ENOLATE OF CYCLOHEXANONE WITH ETHYL IODIDE IN 1,2-DIMETHOXYETHANE AT 29.95°

| $(Enolate)_o$[a] | $(EtI)_o$[a] | Average Initial Rate[b] |
|---|---|---|
| 0.02329 | 0.5000 | 1.345 |
| 0.02799 | 0.5000 | 1.546 |
| 0.03669[c] | 0.5000 | 1.549 |
| 0.04630 | 0.5000 | 1.878 |
| 0.06965 | 0.5000 | 2.337 |
| 0.07891 | 0.5000 | 2.338 |

[a]Initial molar concentration of reactants. [b]Rate in ((mol/l)/sec) x $10^5$. [c]Contained 0.053 M lithium perchlorate.

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